A Stereochemical Comparison Between Radical Atom Transfer Cyclizations and Organozinc Cyclizations of Primary and Secondary Hexenyl Iodides

by

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Cyclized hexenylzinc iodides have been reported to give different *cis:trans* product ratios than the analogous radical cyclized hexenyl iodides and this has been taken as evidence that the organozinc and not radical cyclizations are involved. Unfortunately, temperature dependence was not taken into account when comparing the two sets of ratios. To further investigate these differing *cis:trans* ratios, three hexenyl iodides were synthesized and cyclized under radical atom transfer conditions between 5 °C and 80 °C. The resulting *cis:trans* product ratios were measured by gas chromatography. The *cis:trans* ratios observed ranged from high (i.e. *cis:trans* 1:13.3) to low (*cis:trans* 2.0:1); the selectivities decreased as the temperature increased. Comparison of *cis:trans* ratios of the products from the zinc cyclization to the *cis:trans* ratios of the products from the radical cyclizations at the same temperatures showed that the two sets of ratios were within experimental error of each other. It was concluded that the zinc mediated cyclizations of primary and secondary alkenyl iodides to give cyclopentylmethylzinc halides involve radical cyclizations.

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PREFACE

I would like to start out by thanking Dr. Curran for giving me the opportunity to grow both professionally and personally in his group. I am extremely fortunate to have studied under a person who demonstrates not only immeasurable scientific knowledge, but also impeccable professionalism. Secondly, I would like to thank Professors Cohen and Floreancig for their guidance and support during my stay here at Pitt. Professor Floreancig's willingness to always lend an ear will never be forgotten. I also want to thank the Curran group members, both past and present. I appreciate both the technical and theoretical help as well as the good times we had daily on the eleventh floor.

To say that Professor Richard Hark of Juniata College played a role in my scientific journeys would be a huge and unfair understatement. I owe more to him than I could ever pay back in a lifetime. He never settled for less than my best, even when I would and also showed me that there is a vast world out there other than the science building. I will never forget our Schloss tour in Germany, the chocolate mousse, operas, or the never ending house construction. For all things science and not, I thank him (and Memory!) from the bottom of my heart.

To Judy Iskowitz, my high school chemistry teacher who started it all. I would not have written this thesis if it was not for her encouragement for me to go into the sciences and that phone call to Dr. Dahlberg. She was an inspiration then and still is today. Thank you.

Lastly, I want to thank my friends and family that I have never left my side during this entire process. They are a tremendous source of encouragement and support and without them I would not have been to accomplish any of the goals that I had set. Most importantly, I want to thank Adam Ramsey who has been an unwavering pillar of love and support during this process. Never without a word of encouragement, I could always count on him to listen when things did not work or high five me when they did. Here is to many more high fives with you!

1.0 BACKGROUND AND INTRODUCTION

1.1 RADICAL REACTIONS

Some of the most important reactions in organic chemistry are radical reactions, which are the chemical processes involving unpaired electrons. Though the term "radical" was used before him, Dr. M. Gomberg was the first to produce a triphenylmethyl radical from triphenylchloride and various metals.[1] Though not teeming with popularity at the time, radical reactions play an important role in modern day chemistry. This resurgence is due, partially, to the hard work and tenacity of several physical organic chemists who painstakingly measured the absolute rates for some of the most useful radical reactions.[1, 2] With this information, it was clear to synthetic organic chemists the incredible potential radical chemistry had to further their research.

Radical reactions differ from ionic reactions in that after radical bond cleavage there are two neutral species, each with one odd electron as opposed to one anionic and one cationic specie normally seen with ionic bond dissociation. Typically, radical reactions are started or initiated with what is referred to as homolytic bond cleavage. Radical reaction mechanisms are written with single-headed, or fishhook arrows to denote the movement of only one electron; two radical species are the result. Ionic bond dissociation, on the other hand, usually proceeds with heterolytic bond cleavage. Ionic mechanisms are written with double-headed arrows to signify the movement of two electrons forming one cationic and one anionic specie (Figure 1-1).

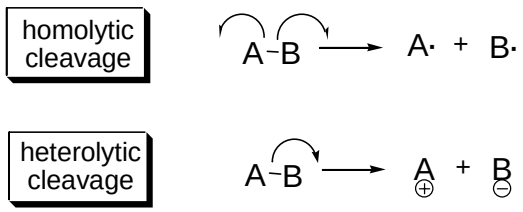


Figure 1-1. Radical homolytic cleavage of A and B as compared against ionic heterolytic cleavage.

One of the most common types of radical reactions involves what is called the chain mechanism. This process involves several steps—initiation, propagation and termination (Figure 1-2).

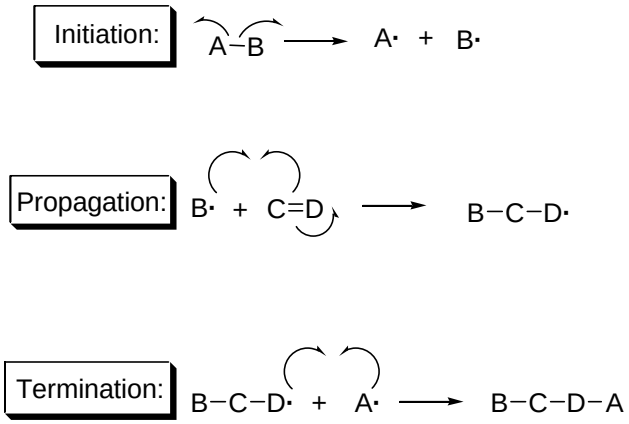


Figure 1-2. Radical chain mechanism using one propagation step.

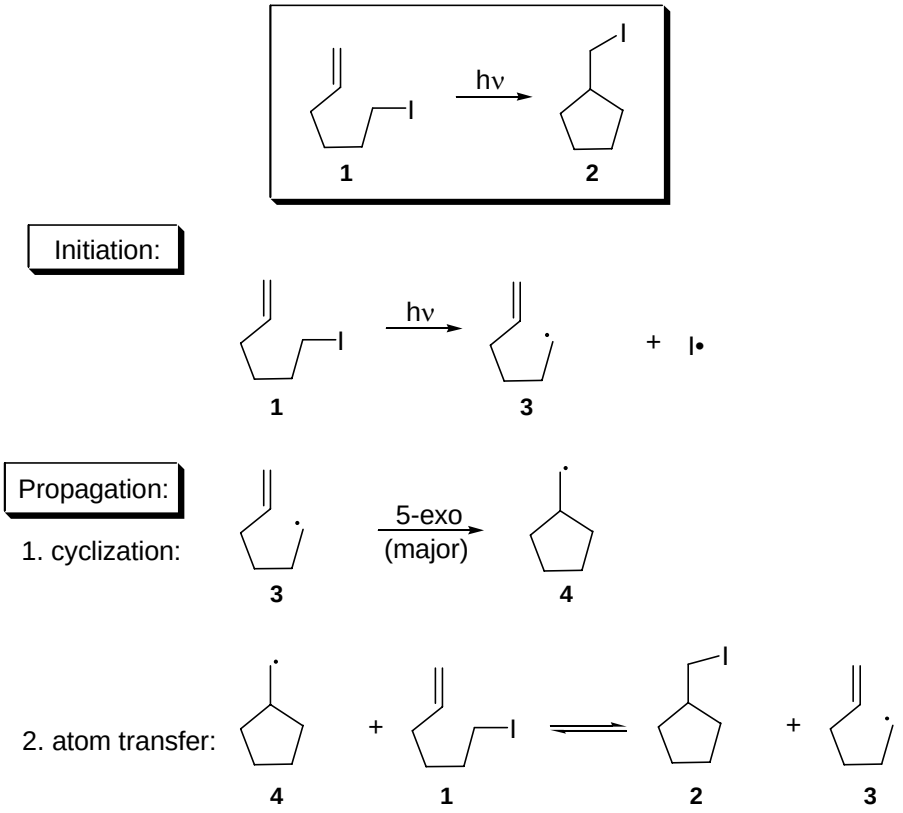
The initiation step is when a non-radical compound is transformed into a reactive radical specie. Radical initiation can occur by either redox, photochemical or homolytic cleavage of a chemical initiator. Most often the latter method is used to give two radicals. The last, or termination step is when two radical species react to form a non-radical compound.[3]

The most important part of the chain mechanism are the propagation steps. Propagation steps represent the middle stage of the process and involve the reacting of a radical with a non-radical to form another radical; for every odd electron on the left side of the arrow is another odd electron on the right side of the arrow. Propagation steps can be inter- or intramolecular and many are the core to all radical chain mechanisms.[3] The rate of the propagation steps are important because the intermediate radical must live long enough to continue to chain. The propagation steps require high chemoselectivity.[3]

There are two types of propagation steps: additions to π-bonds and atom or group transfers. This thesis deals with addition and atom transfer reactions.

1.1.1 Atom Transfer Process

Group or atom radical transfer processes are immensely important when it comes to synthetic chemistry.[4-6] A common atom transfer radical cyclization reaction is seen in Scheme 1-1.



Scheme 1-1. A general 5-hexenyl radical atom transfer process using a hexenyl iodide.

Although functional groups such as xanthates and hydrogen atoms can be transferred via a radical, halogen transfer is a great option because of its broad synthetic scope. In addition to the inter- or intramolecular C-C bond formation, the halogen in the end product leaves a handle for future chemical transformations.[1] The reactivities of the halogens toward a transfer increase in the order of Cl<Br<I; this trend is expected when one considers bond strength and polarizibility.[7] There are limitations to the atom transfer process and they can occur in step 2 of Scheme 1-1. This step must be fast enough so the produced cyclopentylmethyl radical **4** does not add to the double bond of the acceptor molecule (also the starting material in Scheme 1-1). This

exothermic reaction path can be achieved by making sure that the formed radical is more reactive than the initial radical. In Scheme 1-1, the resultant primary radical **3** is more reactive than the initial secondary radical **4**.[3]

Commonly used conditions for the initiation of the iodine atom transfer process can involve the use of light, peroxides, or even triethylborane/oxygen. The initiator, however, that has been found to be the best is bis(tributyltin) because it serves as a scavenger for both atomic iodine (formed in the initiation step of Scheme 1-1) and molecular iodine.[7] The bis(tributyltin) is added to a specified concentration of starting iodine and appropriate solvent. The reaction mixture is then irradiated with visible light to initiate the radical process.

Though planning complex ionic reactions through reaction rates is nearly impossible and only slightly more feasible with pericyclic reactions, it is imperative to synthetic planning that one takes into account the reaction rates of the main and other possible competing radical reactions. Moreover, there is ample literature describing the absolute rate constants of many prototypical radical reactions at various temperatures.[3] Rate constants can be applied to radical reactions carried out in different solvents as the rates of radical reactions show only a small dependence on solvent, especially if the solvents are relatively close in polarity. The rate constant for the common 5-hexenyl radical cyclization is 2.5×10^5 s^{-1} at 25 °C.[8] Monohalogenated precursors such **1** in Scheme 1-1 are typically reacted at a concentration of 0.3 M for atom transfer processes. This higher-than-normal concentration is more beneficial than detrimental as the precursor of **2** is the iodine donor.

The most commonly studied class of radicals is the 5-hexenyl radical as shown in Scheme 1-1 and Figure 1-3. This parent radical as well as substituted 5-hexenyl radicals have been used in many rate studies and a lot is known about their mechanistic and synthetic abilities, including the stereochemical outcome of the 5-*exo* cyclizations for which it is commonly used.[9] These cyclizations are irreversible between normal reaction temperatures (-80 °C to +120 °C) and the 5-*exo* cyclization product **4** is more common than the 6-*endo* cyclization product **5** mainly due to the stereoelectronic reasons (Figure 1-3).

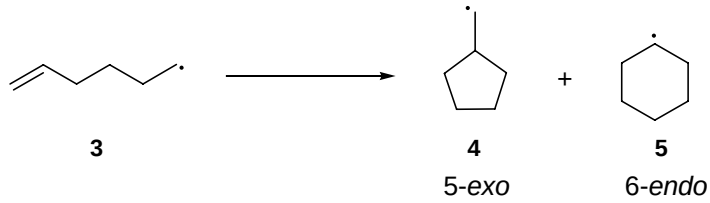


Figure 1-3. The possible 5-*exo* and 6-*endo* products of the 5-hexenyl radical cyclization. The 5-*exo* product 4 is usually the major product of such cyclizations.

1.1.2 Stereoselectivity of 5-Hexenyl Radical Cyclizations

The three precursors used in this study that led to the substituted 5-hexenyl radicals were primary and secondary iodides **6-8** (Figure 1-4). Upon radical atom transfer cyclization, both the *cis* or *trans* isomers of 1,2-disubstituted cyclopentylmethyl radicals are obtained. The ratio of *cis* and *trans* products can change depending upon the substitution pattern of the precursor and reaction temperature.

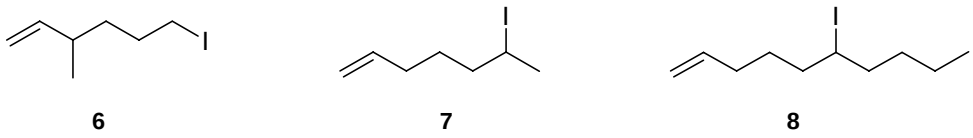


Figure 1-4. Primary and secondary iodide atom transfer cyclization precursors.

In the case of the primary iodide **6**, the *trans* isomer of the cyclized product dominates[10] whereas the *cis* cyclic product is the major isomer of the secondary iodides **7** and **8**.[10] The transition states of these cyclizations are based on the Beckwith-Houk model and can go through either a chair-like or boat-like conformation (Figure 1-6). All references to numbered carbons in this thesis will be related back to the numbering system shown in Figure 1-5.

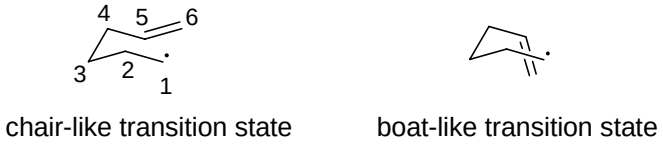


Figure 1-5. Chair-like and boat-like transition states for 5-hexenyl radical cyclizations.

These transition states resemble the cyclohexane chair structures. In both the chair and boat, the C1 and C5 bond length in the cyclized product is calculated to be "stretched" at 2.2 – 2.3 Å, which is longer than its equilibrium length of 1.5 Å. This longer length is almost the same as the distance between the C1-C3 atom distance across the ring in both the chair and boat, but more importantly, releases both torsional and angle strain that will be present in the final cyclopentane product. Other atoms (C2, C3 and C4) in the transition states very closely resemble their cyclohexane equivalent. Both the chair and boat have distinct "axial" and "equatorial" substituents.[9]

Using this model as a general guideline can make predicting stereochemical outcomes easier for substituted compounds. With the addition of a stereocenter, there can be four transition states that arise: chair-equatorial, boat-equatorial, chair-axial and boat-axial (Figure 1-6).

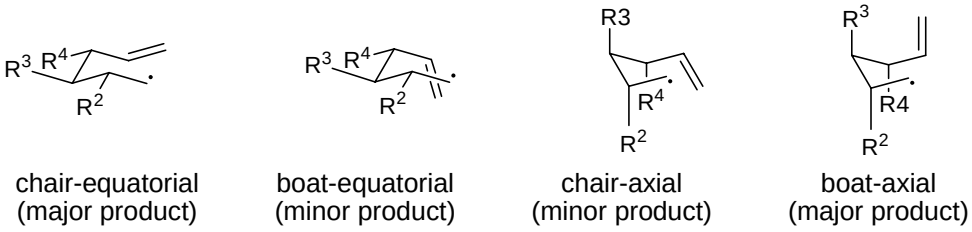


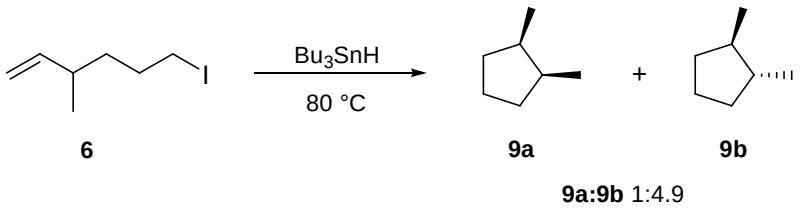
Figure 1-6. Chair and boat transition states with introduction of substituents.

For monosubstituted systems, the major product comes from mainly the chair-equatorial transition state. Though too high in energy to be a significant contributor, the disfavored boat-axial transition state will also lead to the major product. The minor products come from either one or more likely both the boat-equatorial and chair-axial transition states.[9]

1.1.2.1 *4-Substituted Hexenyl Radicals*

As noted earlier, the 4-substituted hexenyl radical mainly yields the *trans* isomer of disubstituted cyclopentanes. As a class, 4-substituted hexenyl radicals tend to have the greatest selectivity of all simple hexenyl radicals.[9] The major *trans* isomer **9b** is the product expected according to the Beckwith-Houk model and the selectivity that can be achieved using Bu_3SnH is *cis:trans* 1:4.9 at 80 °C (Eq. 1-1). With other 4-substituents, selectivities of *cis:trans* 1:19 or higher are common.[9] For this thesis, all *cis*-1,2-disubstituted cyclopentane are denoted by an **a** after the compound's number. Accordingly, all *trans*-1,2-disubstituted cyclopentanes have a **b**

after their corresponding number. All ratios are reported as *cis:trans* even if the *trans* product is the major isomer.

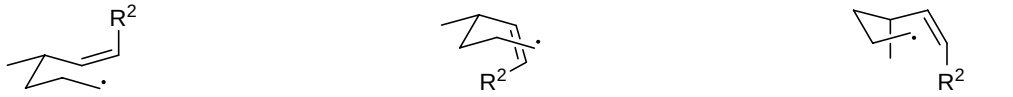


6 **9a** **9b**

9a:9b 1:4.9

(1-1)

The good to excellent *trans*-selectivities can be explained by A-strain.[11] The chair-equatorial transition state has the lowest in energy as it minimizes A-strain (Figure 1-7). The allylic C4-C5 bond position is near the energy minimum as determined by A-strain. On the other hand, both the boat-equatorial and chair-axial transition states demand less favorable allylic bond positioning. This unfavorable bond disposition leads to higher energy relative to the chair-equatorial transition state energy. *Z*-Disubstituted alkenes normally give very high selectivities, lending more evidence to the importance of A-strain.[9]



chair-equatorial (minimizes A-strain)

boat-equatorial (C=C gauche to two C-C)

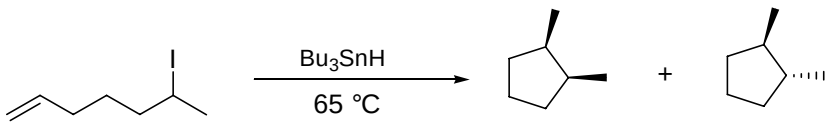
chair-axial (C=C eclipses Me)

Figure 1-7. Transition states for 4-substituted hexenyl radicals. The selectivities are good if R^2 = H and excellent is $R^2 \neq$ H.

1.1.2.2 *1-Substituted Hexenyl Radicals*

Not as selective as the 4-substituted hexenyl radical, the 1-substituted radical can lead to a wide range of disubstituted cyclopentane *cis:trans* ratios depending on the substituent, with the *cis* isomer usually being the major one. The behavior of the parent 1-methylhexenyl radical, formed from **7**, is typical for many 1-substituted hexenyl radicals of this class. Though the *cis* product dominates, the ratio can be fairly small. For example, reductive cyclization of **7** with Bu_3SnH at 65 °C gives **9a** and **9b** in a 1.9:1 (Eq. 1-2).[9] The selectivity of *cis* over *trans* is not high because the difference in energy for the chair-like and boat-like transition states for the 1-substituted hexenyl radical cyclizations is less than 1 kcal/mol.[12] This small energy difference

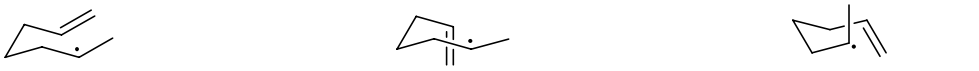
makes it easy for the transition state to become perturbed (i.e. anomeric effects or the presence of Lewis acids) and adopt another conformation.[1]



7 **9a** **9b** (1-2)

9a:9b 1.9:1

According to the Beckwith-Houk transition state model, the major *cis* isomer **9a** comes from the chair-equatorial transition state whereas the boat-equatorial and chair-axial transition states (Figure 1-8) both contribute to give the minor *trans* isomer **9b** found in Equation 1-2.[13]



chair-equatorial (give *cis* product) | boat-equatorial (give *trans* product) | chair-axial (gives *trans* product)

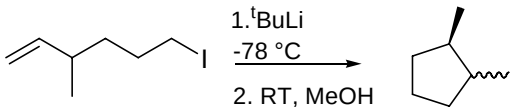
Figure 1-8. Transition states for 1-substituted hexenyl radicals.

The reasons for the *cis* selectivity of these 1-substituted hexenyl radical cyclization products have been discussed heavily because in the chair-equatorial transition state, the methyl and methylene groups are nearly eclipsed. This disposition should lead to the *cis* product being disfavored. Calculations of Spellmeyer and Houk give reason to the contrary as the forming bond is sufficiently long to negate the nearly eclipsing action of the methyl and methylene group; the energetic penalty being less than 1 kcal/mol.[13] These calculations also put forward that the "axial" substituent on C1 is all but eclipsed with the hydrogen on C2 and the "equatorial" substituent is *anti* to the C2-C3 bond while the axial substituent is gauche. These factors considered together are believed to be the reasoning behind the *cis* isomer being the major one.[9]

1.2 ORGANOZINC HALIDES

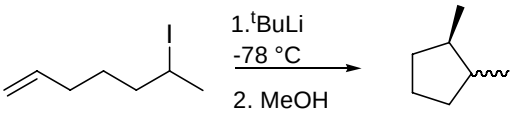
The synthetic need to prepare functionalized organometallic compounds is extremely important. These organometallic reagents are useful in the preparation of complex organic molecules since they can lead to shorter reaction routes.[14] For example, their use can do away with the costly protection-deprotection steps often needed. Also, the use of organometallic reagents led to the discovery of new reactivity patterns including ring closures, which result from the carbon chain linking the carbon-metal bond to the functional group being sufficiently long.[14]

Carbometallation describes the reaction of a organometallic reagent with alkyne, alkene, allene or related substrate.[15] The first example of a carbometallation reaction described appears to have been in 1927 by Bahr and Ziegler.[16] Some commonly used organometallic reagents are organomagnesium and organolithium reagents. These reagents have a high reactivity and are able to add to carbonyl groups (i.e. Grignard additions) as well as alkenes, albeit more slowly.[17, 18] As seen in Equations 1-3 and 1-4, hexenyl iodides **6** and **7** can be transformed into the analogous lithium reagents by lithium-iodide exchange. They cyclize upon warming to give **9a** and **9b** after protonation in 1:13.6 and 1:44 ratios, respectively.[19] The cyclization proceeds via a known anionic mechanism and such high stereoselectvities of the cyclized products are common among this class of reactions.



6 → **9**
9a:9b 1:13.6

(1-3)



7 → **9**
9a:9b 1:44

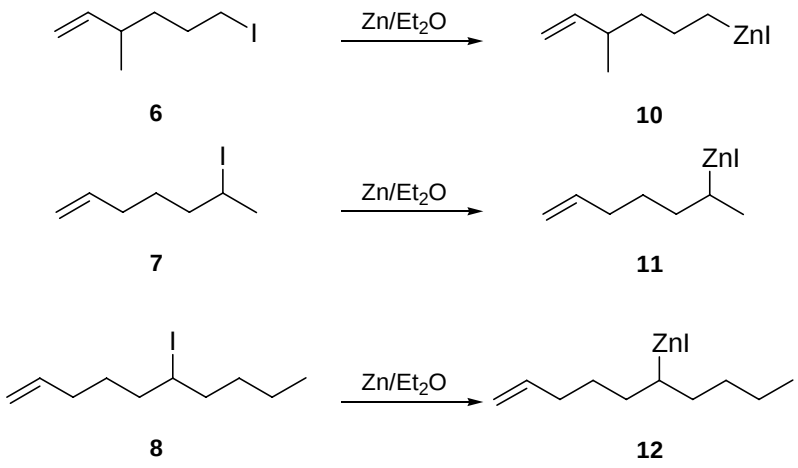
(1-4)

Organozinc compounds were initially discovered in 1849 by Frankland when he produced pyrophoric diethylzinc by heating ethyl iodide with zinc. Though popular at the time, the interest in organozinc compounds decreased as more reactive organomagnesium and

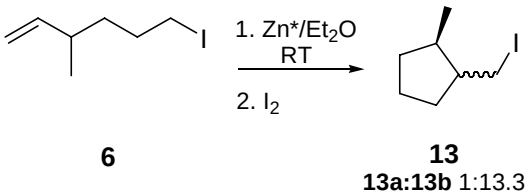
organolithium reagents began to surface. A resurgence of interest began when it was established that this lack of reactivity could be used in a productive synthetic manner. The reason for the low reactivity of organozinc compounds is the high covalent character of the carbon-zinc bond, which, in turn, is the reasoning for the creation and use of high functionalized organozinc compounds.[14, 20]

There are several general procedures for zinc insertion into the carbon-halide bond (R-X → R-Zn-X, Scheme 1-2). The method used for a given route is dependent upon several variables including the nature of the organic moiety, the halide, the reaction conditions such as solvent, concentration and temperature, and lastly the zinc activation. Zinc foil and powder as well as diethyl zinc and activated zinc created *in situ* (Rieke zinc) are all commonly used zinc insertion reagents.[21-24]

Of specific interest to this thesis is whether organozinc halide compounds **10**-**12** cyclize or not and if so, then how. A zinc mediated cyclization of hexenyl iodide **6** using activated zinc made *in situ* at room temperature resulting in *cis:trans* product ratio of 1:13.3 is shown in Equation 1-5.[25]

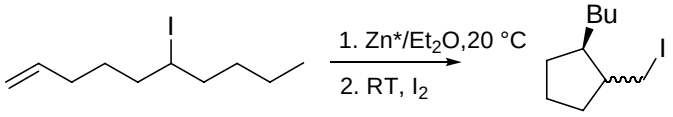


Scheme 1-2. Organozinc halide precursors under discussion for possible radical mechanism of cyclization to disubstituted cyclopentanes.



(1-5)

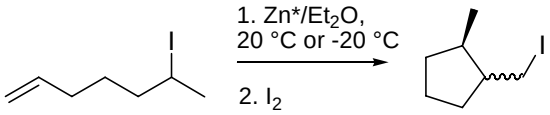
The zinc mediated cyclization of **8** gave a product ratio of **14a:14b** 4.0:1 upon slow warming to room temperature before iodine quenching (Equation 1-6). This *cis:trans* ratio differs from the reductive radical cyclization ratio of **14a**:**14b** 1.5:1 using Bu_3SnH at 80 °C cited in the Meyer et *al.* article.[25]



8 **14**
14a:14b 4.0:1

(1-6)

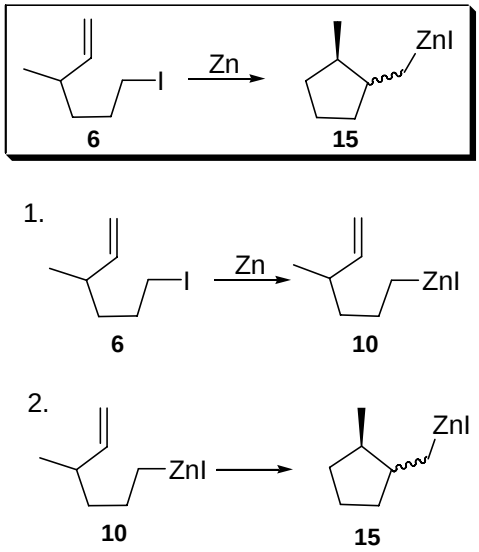
The zinc mediated cyclization of **7** resulted in a *cis:trans* ratio of **13a:13b** 4.3:1 using activated zinc made *in situ* at both 20 °C and -20 °C (Equation 1-7). This result is different from organolithium and organomagnesium carbocyclizations which gave the *trans* product as the observed isomer. These results hinted at a radical reaction as opposed to the anionic mechanism.[19, 26]



7 **13**
13a:13b 4.3:1

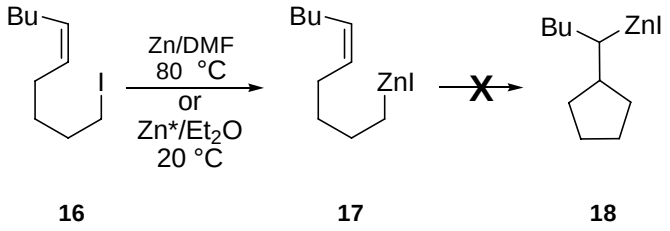
(1-7)

The mechanism in which the cyclization of the organozinc halide goes through is under much debate, specifically between an anionic or radical pathway. Meyer and colleagues concluded that because the zinc-mediated cyclization of **6** (Equation 1-5) had a high selectivity similar to the intramolecular carbolithiation cyclization of **6** (Equation 1-3) the mechanisms should also be the same—anionic (Scheme 1-3).[25]



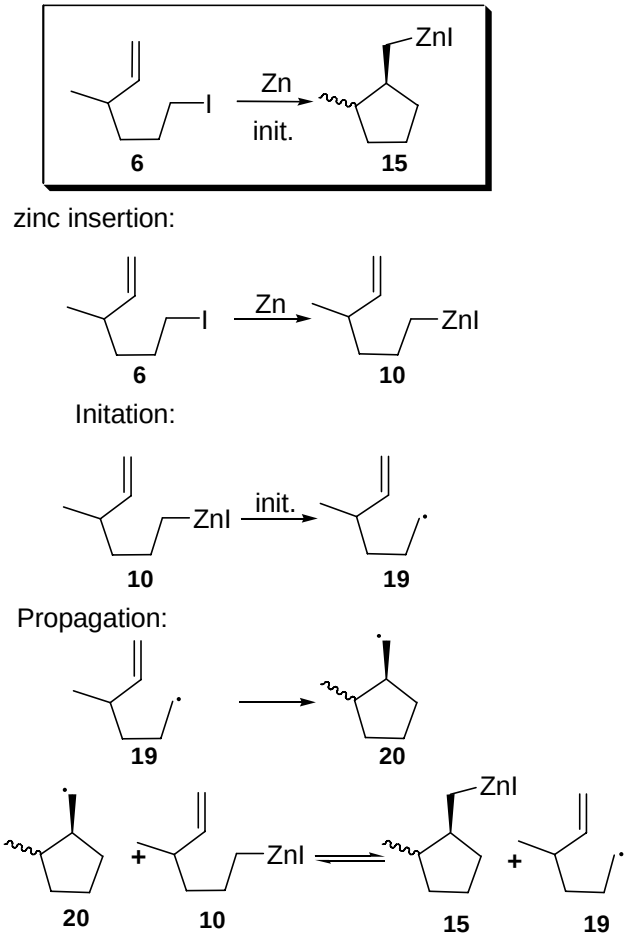
Scheme 1-3. Anionic mechanism proposed by Meyer et *al.* using hexenyl iodide 6.

Additionally, the authors described the inability of organozinc halide **17** to cyclize to give **18** after sitting at room temperature for 12 h (Scheme 1-4). Also, the pure *Z* stereochemistry of the alkene did not change during the 12 h. Meyer and his colleagues claim that if a radical species would have been generated at any point of the reaction, the pure *Z* stereochemistry of the alkene would have been reduced as a result of partial equilibrium with the *E* isomer.[25]



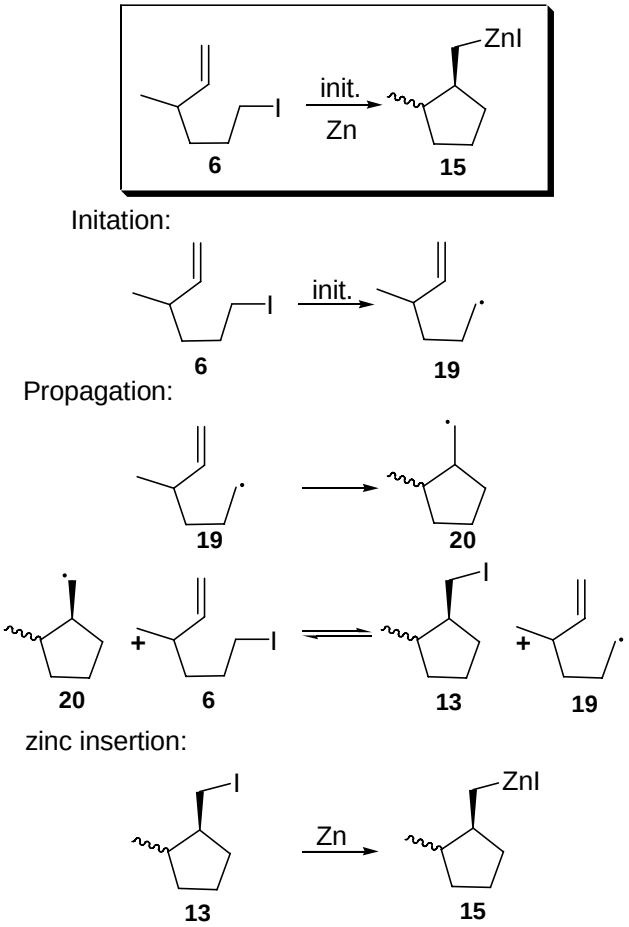
Scheme 1-4. The inability of an organozinc halide to cyclize on a disubstituted alkene.

If the reaction proceeds by a radical mechanism, the zinc can insert into the hexenyl iodide **6** first and then cyclize via a radical group transfer process to give product **15** as seen in Scheme 1-5.



Scheme 1-5. Proposed radical mechanism with zinc insertion of hexenyl iodide 6 before group transfer signifying the presence of a linear organozinc halide.

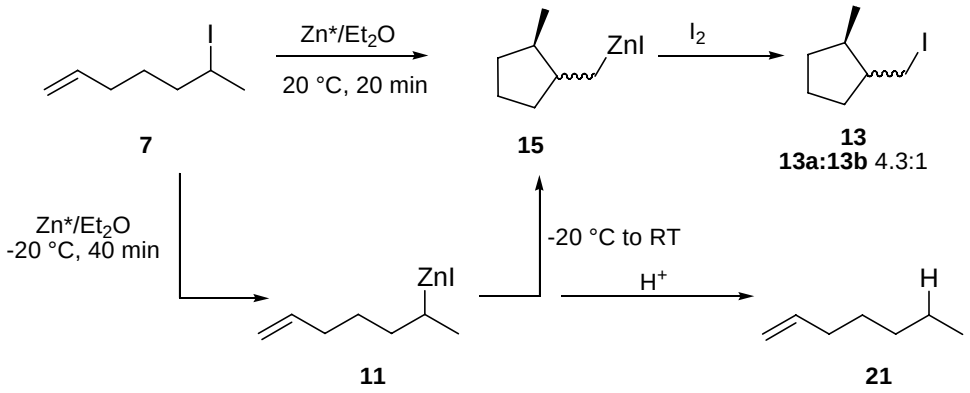
Alternatively, the hexenyl iodide **6** can cyclize by a radical atom transfer process first to give **13** into which the zinc can insert to give **15** as shown in Scheme 1-6. These two possibilities beg the question of when does zinc insertion take place if a radical cyclization is involved?



Scheme 1-6. Proposed radical cyclization with zinc insertion after radical atom transfer cyclization occurs.

Crandall and Ayers observed a 1.1:1 mixture of (*E*)- and (*Z*)-vinyl iodides when an analogous secondary iodide was reacted under radical conditions using bis(tributyltin). The same ratio of isomeric vinyl iodides was obtained when the iodides were cyclized using zinc and ultrasound.[27] The authors concluded that the zinc mediated cyclization, due to the same isomeric product ratios of the vinyl iodides were radical in nature.

Furthermore, Meyer and colleagues provided evidence through hydrolyzed aliquots of a clean and rapid oxidative insertion of the activated zinc into the carbon-iodine bond of **7** leading to the acyclic organozinc halide **11** via gas chromatography (Scheme 1-7).[25] The authors, therefore, concluded that the zinc does insert into the alkyl halide before cyclization thus forming a linear organozinc halide Upon warming to room temperature, the linear organozinc halide cyclized, which lead Meyer et *al.* to hint at a non-radical mechanism.[25]



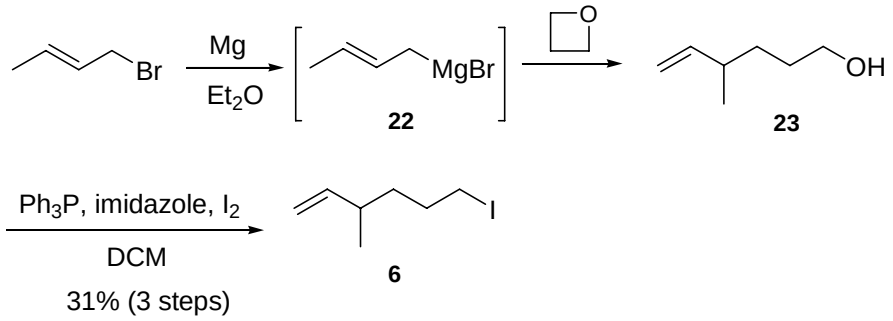
Scheme 1-7. Zinc insertion and cyclization of 7 to 13 showing a linear organozinc halide

2.0 RESULTS AND DISCUSSION

2.1 SYNTHESIS AND CHARACTERIZATION OF HEXENYL IODIDES 6, 7 AND 8

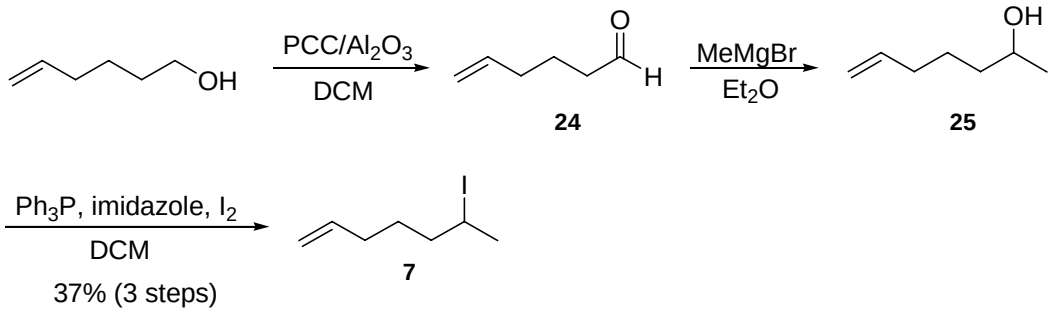
We hypothized that the zinc mediated cyclizations of alkenyl iodides described by Meyer et *al.* might involve radical cyclizations. Three hexenyl iodides were selected for study from the authors' work involving one primary iodide **6** (precursor of a 4-substituted hexenyl radical) and two secondary iodides **7** and **8** (precursors of 1-substituted hexenyl radical). The differences in stereoselectivities described by the authors for the zinc process and those reported by the literature for radical processes might be due to temperature effects. The zinc reactions are usually performed at 25 °C or below while the radical experiments were conducted at 65 °C or above. To better compare authentic radical cyclization stereoselectivities with the Meyer et *al.* results, we needed a detailed understanding of the temperature dependence of the radical reactions. Our plan was to synthesize these compounds, conduct radical atom transfer cyclizations over a range of temperatures, and then compare the *cis:trans* product selectivities observed with those of Meyer's.

The synthesis of **6** started with commercially available crotyl bromide which was transformed into the Grignard reagent **22** by insertion of magnesium. Oxetane was then added to the reaction mixture to give alcohol **23**, which upon workup was very carefully concentrated on the rotary evaporator because it is volatile. Crude alcohol **23** was then iodinated and the resulting iodide was distilled under reduced pressure to give iodide **6** in 31 % over three steps (Scheme 2-1).[10]



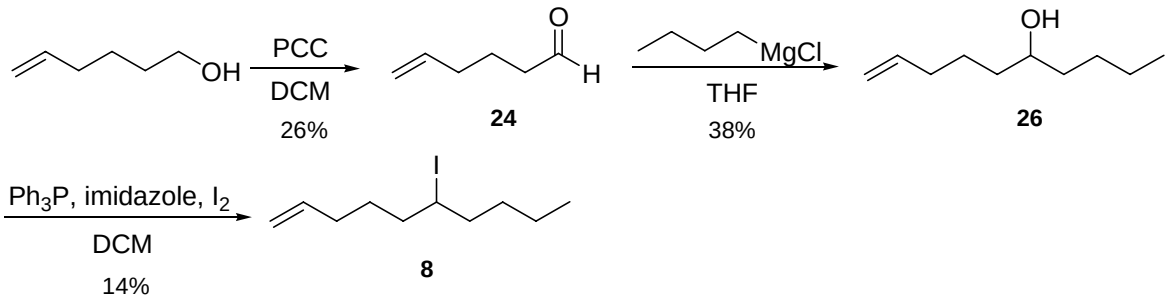
Scheme 2-1. Synthesis of 6-iodo-3-methylhexene (6)

The synthesis of secondary iodide **7** started with commercially available 4-buten-1-ol which was oxidized using PCC on alumina to give aldehyde **24**.[28] Methyl magnesium bromide was added to crude 5-hexen-1-al **24** give the alcohol **25**. For solvent removal, a 10 °C water bath was used for the rotary evaporator because **25** is volatile. The crude alcohol was transformed by iodination into iodide **7** in 37 % over three steps (Scheme 1-7).[29] The product **7** was purified via Kugelrohr distillation.



Scheme 2-2. Synthesis of 6-iodoheptene (7)

Compound **3** was prepared in a similar manner to compound **7**. Commercially available 4-buten-1-ol was oxidized using PCC to yield 26 % of aldehyde **24**.[28] Again, great care was taken while concentrating *in vacuo* because of the high volatility of **24**. The crude 5-hexen-1-al **24** was then transformed into the secondary alcohol **26** in 38 % yield by reaction with butylmagnesium chloride in THF. Crude alcohol **26** was then iodinated and purified by Kugelrohr distillation to give secondary iodide **8** in 14 % yield. (Scheme 2-3).[29]

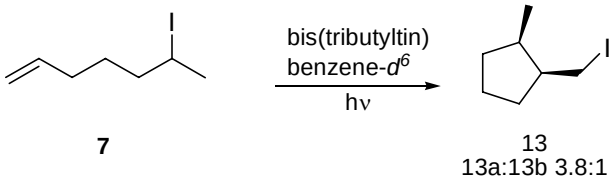


Scheme 2-3. Synthesis of 6-iododecene (8)

Both crude and purified compounds were characterized by ^{1}H NMR spectroscopy to verify their structure and purity. All final hexenyl iodides were injected into the gas chromatograph to also check for purity and determine retention times. Aliquots taken from reaction mixtures were also injected into the gas chromatograph to monitor reaction progress. The reaction products, 1,2-disubstituted cyclopentanes, were characterized via ^{1}H NMR spectroscopy and compared against the reported ^{1}H NMR resonances obtained by Meyer and colleagues to ensure product formation.

2.2 TEMPERATURE DEPENDENT CYCLIZATIONS OF HEXENYL IODIDES 6, 7 AND 8

With three iodide precursors **1-3** in hand, we studied the cyclization of these compounds using radical conditions to yield **9** and **11**. An example of a typical reaction is the radical cyclization of hexenyl iodide **2** at 35 °C to **9a** and **9b** that resulted in a *cis:trans* ratio of 3.8:1 (Eq. 2-1). An NMR tube containing a 0.3 M solution of **2** dissolved in benzene-d_6 (0.5 mL) and 10 mol % of bis(tributyltin) under an inert atmosphere was placed in a 500 mL water-filled beaker equipped with a thermometer and held approximately 5-10 cm from the 275 W sunlamp with a small clamp.



(2-1)

The water in the beaker was already equilibrated to the temperature of light coming from the lamp, which was 35 °C and kept uniform by a stirring paperclip. Aliquots of 10 μL were periodically removed, diluted with 1 mL of dichloromethane and injected (5 μL) into the gas chromatograph to determine if the reaction progress and the *cis:trans* ratio of the products. The sample that indicated a complete reaction was then analyzed via ^{1}H NMR spectroscopy. A reaction was considered complete and therefore stopped when two peaks with slightly longer retention times than the starting material were present and all starting material was consumed as seen in Figure 2-1. The gas chromatogram shows the *cis* and *trans* product peaks for reaction of **7** to **13** at 35 °C for 45 minutes. The ratio of areas indicate the *cis:trans* ratio of 3.8:1. The starting hexenyl iodide **7** at 4.2 minutes is absent, so all starting material is consumed. For all reactions, the gas chromatograms show two product peaks except where stated.

To obtain the different reaction temperatures ice was manually added to the beaker for all temperatures under 35 °C, including 25 °C. During the course of the reactions, the temperature varied 2-3 °C in either direction. For the reaction temperature of 80 °C an oil bath heated to approximately 45 °C was used as the heat emitting from the lamp raised the oil bath temperature to 80 °C. Once the oil bath was at 80 °C, the NMR tube was placed into the bath. All hood sashes were covered with aluminum foil and a foil covered blast shield was placed around the reaction set-up for precaution and safety reasons.

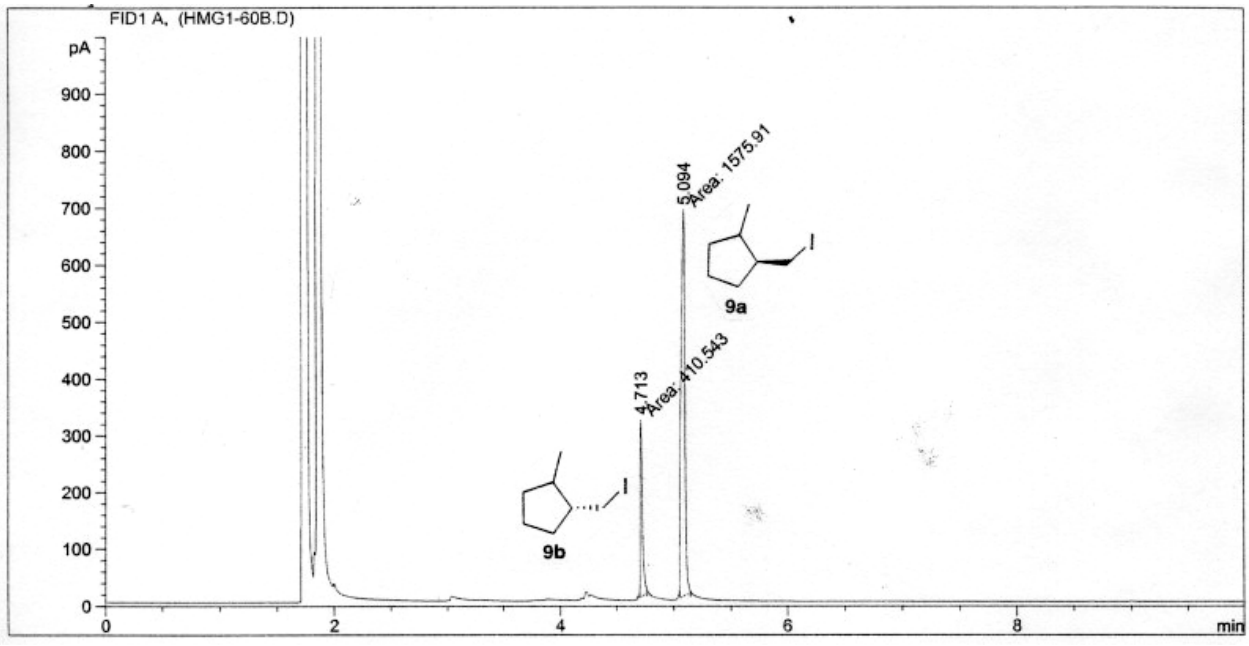
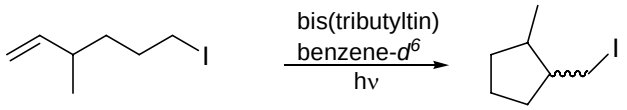


Figure 2-1. A typical GC used in determining *cis:trans* ratios. This GC is of the cyclization of 7 to 13 at 35 °C for 45 min. The retention time for 7 is 4.2 min.

2.3 RADICAL ATOM TRANSFER CYCLIZATION OF 6 TO 13

The atom transfer cyclization of primary iodide **6** gave **13b** as the major product (Eq. 2-2), but there was a decrease in selectivity as the temperature increased (Table 2-1). Starting at 5 °C, the *cis:trans* selectivity was very good at 1:13.3 (Entry 1). Increasing the temperature to 15 °C, 25 °C and 35 °C saw *cis:trans* ratios of 1:11.5, 1:9.0 and 1:7.0, respectively. The highest temperature used for the cyclizations was 80 °C and the complete reaction at 420 minutes gave a low selectivity of 1:2.0 (Entry 7). There were several aliquots removed and analyzed at various reaction times for the 80 °C reaction. Entries 5-7 show that with increased reaction time, the *trans* selectivity decreased (i.e. the amount of *cis* isomer increased). This result suggests that upon longer reaction times at 80 °C, the *trans* isomer begins to decompose as seen in the corresponding gas chromatograms (Appendix B).



(2-2)

6

13a = *cis*
13b = *trans* (major isomer)

Table 2-1. Data for cyclization of 6 to 13.

Entry	Temperature (°C)	Time (min)	% Conversion	*cis:trans* 13a:13b
1	5	270	100%	1:13.3
2	15	210	100%	1:11.5
3	25	150	100%	1:9.0
4	35	120	95%	1:7.0
5	80	240	48%	1:4.5
6	80	300	80%	1:3.5
7	80	420	95%	1:2.0

The *cis:trans* ratio of **13** at 80 °C for 300 minutes is 1:3.5 and is the same ratio observed under radical conditions by Beckwith[30] This result shows that the radical method used was accurately performed. In Entry 3, a *cis:trans* ratio of 1:9.0 was obtained at 25 °C whereas Meyer et *al.* observed a *cis:trans* ratio of 1:13.3 at 25 °C.[25] The selectivities obtained via radical conditions are very close to results of Meyer and colleagues. Though the ratios do not match exactly, they are within experimental error and show the same *trans* selectivity.

Chart 2-1 plots the natural log of the *cis:trans* ratios of **13a:13b** against temperature to get a linear relationship. Using Chart 2-1, other *cis:trans* ratios can be predicted at various temperatures with confidence. Though there are three data points for the reaction at 80 °C, only information from Entry 7 was used for the making of Chart 2-1.

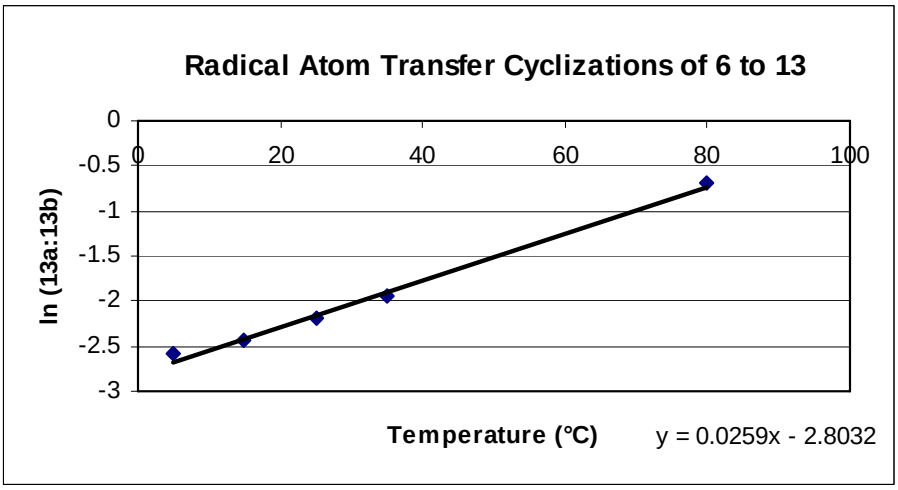


Chart 2-1. Linear relationship between the ln(*cis:trans* 13a:13b) and temperature.

2.4 RADICAL ATOM TRANSFER CYCLIZATION OF 7 TO 13

The cyclization of secondary iodide **7** to yield **13a** as the major product (Eq. 2-1) had a *cis:trans* ratio of 4.9:1 at 5 °C (Table 2-2, Entry 1). Though the major product isomer is different from the cyclization of the primary iodide **6**, the selectivity also decreased as the temperature increased in the primary iodide case. Also, the variation over the temperature range is not as large as with the primary iodide **6** cyclization. Temperatures of 15 °C, 25 °C and 35 °C gave *cis:trans* ratios of **13a:13b** 4.8:1, 4.3:1 and 3.8:1, respectively (Entries 2-4). The *cis:trans* ratio at 80 °C is moderate at 2.7:1 (Entry 5).

Table 2-2. Data for cyclization of 7 to 13.

Entry	Temperature (°C)	Time (min)	% Conversion	*cis:trans* 13a:13b
1	5	90	100%	4.9:1
2	15	75	100%	4.8:1
3[a]	25	45	100%	4.3:1
4	35	45	100%	3.8:1
5	80	90	100%	2.7:1

a. Experiment also performed in Et_2O and gave the exact same *cis:trans* ratio of 4.3:1.

The ratio of 2.7:1 at 80 °C is the same as the *cis:trans* ratio observed under radical conditions at 74 °C by Brace.[31] Again, this confirms that the technique used is correct. Meyer et *al.* saw the same selectivity of **13a:13b** 4.3:1 with their secondary organozinc cyclization at 25 °C that was observed under radical conditions. [25, 32, 33] These consistencies show strong evidence toward a radical mechanism of the organozinc cyclizations.

Additionally, an experiment was performed to show the effects, if any, solvent might have on the *cis:trans* ratios. Meyer and colleagues used Et_2O as the solvent for their organozinc cyclizations and the radical experiments done for this thesis were done in benzene-d^6. Stereoselectivities in radical reactions are not thought to be very solvent dependent.[9] We tested this notion by conducting our radical cyclization of **7** in Et_2O. The radical cyclization of **7** to **13** was performed at 25 °C in Et_2O and at 60 minutes, the reaction was complete and gave the same *cis:trans* ratio of 4.3:1 as with the benzene-d^6 solvent. This result suggests that our radical cyclization results in benzene-d^6 can be directly compared with the authors cyclization results in Et_2O

Chart 2-2 plots the natural log of the *cis:trans* ratios of **13a:13b** against temperature to get a linear relationship. Using Chart 2-2, other *cis:trans* ratios can be predicted at various temperatures with confidence.

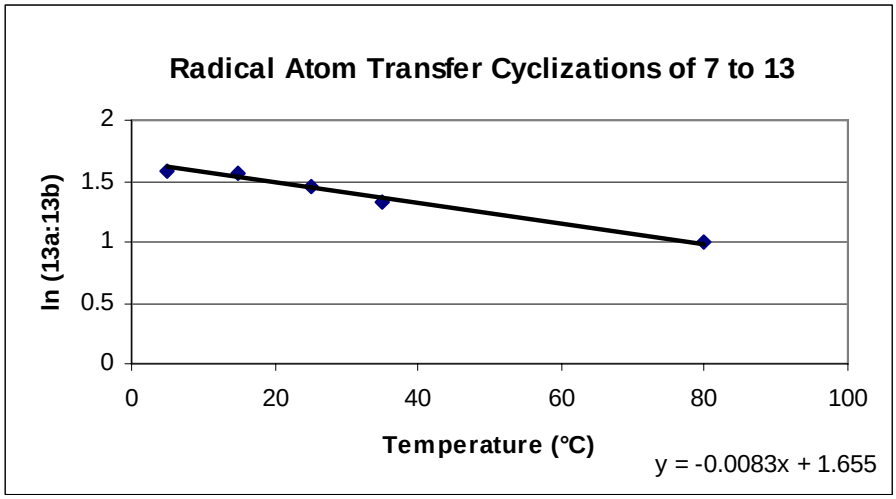
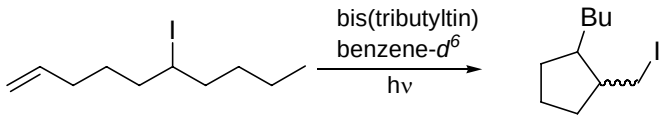


Chart 2-2. Linear relationship between the ln(*cis:trans* 13a:13b) and temperature.

2.5 RADICAL ATOM TRANSFER CYCLIZATION OF 8 TO 14

The atom transfer cyclization of the other secondary iodide **8** gave product **14a** as the major product (Table, 2-3, Eq. 2-3). The *cis:trans* ratio at 5 °C was 3.2:1 (Entry 1) and continued to decrease, though not greatly, as the temperature increased. The *cis:trans* ratio at 20 °C was 3.1:1 and at 80 °C was 2.3:1 (Entries 2 and 3).



8

14a = *cis* (major isomer)
14b = *trans*

(2-3)

Table 2-3. Data for cyclization of 8 to 14.

Entry	Temperature (°C)	Time (min)	%Conversion	*cis:trans* 14a:14b
1	5	120	100%	3.2:1
2	20	150	100%	3.1:1
3	80	180	100%	2.3:1

At 80 °C Meyer reported a *cis:trans* ratio of 1.5:1 using tributyltin hydride, whereas the bis(tributyltin) radical cyclization had a selectivity of 2.3:1.[25] Using the zinc-mediated cyclization method, Meyer obtained a *cis* selectivity of 2.7:1 at room temperature, which is also within experimental error to the selectivity obtained with the radical method of 3.1:1 (Entry 2). Again, these similarities in ratios hint strongly to a radical pathway for the organozinc cyclizations.

No chart was created for the cyclizations of **8** to **14** because only three data points were collected.

2.6 CONCLUSIONS

Progress has been made toward the determination of a mechanistic pathway for the cyclizations of organozinc iodides. Gas chromatograms and ^{1}H NMR spectra were used to analyze the radical cyclizations and it was observed that all iodides **6-8**, analogous to the organozinc iodides **10-12**, cyclized with approximately the same *cis:trans* selectivity under radical conditions. The radical stereoisomer ratios were confirmed by selectivities already found in earlier literature. These stereoselective ratios are strong indicators that the organozinc halides cyclize via a radial pathway and not an anionic pathway as previously thought by Meyer and colleagues. Furthermore, it can be concluded that because of the observed ratios and linear organozinc iodide compound that Mechanism III is the cyclization pathway for the cyclizations of **10-12**.

Future work includes confirmation that the linear organozinc halide is formed first before cyclization. Oxygen should be removed from the reaction atmosphere and then slowly introduced back into the system. If the zinc does insert before cyclization, the rate of cyclization should accelerate as the oxygen helps radical species form much in the same way as it does with triethylborane to give ethyl radicals.

3.0 EXPERIMENTAL

3.1 GENERAL PROCEDURES

All reactions were carried out under an argon atmosphere in oven-dried or flame-dried glassware. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Toluene, dichloromethane (DCM) and ethyl ether (Et_2O) and THF were all obtained after being dried through an activated alumina column. All other reagents were used as received without further purification from either Sigma-Aldrich, Strem Chemicals or Fisher Scientific.

Flash chromatography was performed on silica gel (230-400 ASTM) purchased from Sorbtech or Bodman. Thin layer chromatography (TLC) was carried out using E. Merck silica gel 60 F_{254} glass backed plates. All hexanes used for flash chromatography were distilled over boiling stones to remove grease. The TLC plates were visualized using standard UV light, phosphomolybdic acid or potassium permanganate staining solution.

NMR spectra were recorded on Bruker model Avance 300 or Avance DPX-300 with ^{1}H at 300 MHz and ^{13}C at 75 MHz. Unless noted otherwise, NMR spectra were taken in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) relative to TMS using the residual solvent proton peak of $CDCl_3$ (7.27 ppm). The following abbreviations are used for reporting splitting patterns: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets.

Gas chromatograms (GC) were run on an Agilent 6850 gas chromatograph using HPCHEM enhanced integrator software. An HP-1 capillary methyl siloxane column of 30 m in length and 0.32 mm in diameter with a 0.25 μm film was used for all runs. GC data is reported with a retention time and % area of the total intergrated area.

3.2 GENERAL CYCLIZATION PROCEDURE

In an NMR tube, the alcohol precursor was dissolved in benzene-d_6 to make a 0.3 M solution. Bis(tributyltin) (10 mol %) was added to the solution and the NMR tube was placed in a 500 mL beaker full of water. The water was stirred with a paper clip to allow for a uniform water temperature. The beaker was placed 5 to 10 cm in front of a GE 275-W sunlamp. The reaction mixture was then irradiated at the specified temperature. For temperatures of 5 °C, 15 °C and 20 °C ice was added to the water bath to maintain the proper temperature. Aliquots of 0.1 mL were removed and analyzed via GC until 95 % to 100 % of the starting alcohol was consumed. A sealed tube in an oil bath was used for the 80 °C cyclization.

3.3 SYNTHETIC PROCEDURES

Compounds **23** and **6** were identified by comparison to spectral data in reference.[10]
Compounds **24**, **25**, **7**, **26**, **8**, **13** and **14** were identified by comparison to spectral data in reference.[25]

4-Methylhex-5-en-1-ol (23).[10]

To a 0 °C suspension of freshly cracked magnesium turnings (7.20 g, 300 mmol) in Et_2O (80 mL) was added dropwise crotyl bromide (9.0 mL, 90 mmol) over 30 min. Once all of the crotyl bromide was added, the mixture was allowed to stir for 10 min. Oxetane (11.70 mL, 180 mmol) was added and the resultant mixture was stirred at 0 °C for 4 h. The mixture was warmed to RT and let to stir overnight. The mixture was cooled to –20 °C and NH_4Cl was added. The mixture was diluted with Et_2O and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator. The residue was purified by column chromatography (20 % EtOAc in hexanes) to yield an oil (1.22 g, 10.7 mmol) in 12 %.

6-Iodo-3-methylhex-1-ene (6).[10]

To a 0 °C solution of triphenylphosphine (5.61 g, 21.40 mmol) and imidazole (1.46 g, 21.40 mmol) in DCM (200 mL) was added portionwise iodine (5.43 g, 21.4 mmol). The mixture was stirred for 10-15 min then warmed to RT for 5 min. To the yellow mixture was added a solution of alcohol **23** (1.22 g, 10.7 mmol) in DCM (12 mL). The resulting mixture was allowed to stir for 3 h and then treated with H_2O (300 mL). The aqueous phase was extracted with DCM (3 x 100 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated on a rotary evaporator. The solid residue was suspended in pentane (300 mL) and then stirred vigorously overnight. The suspension was then filtered and concentrated on a rotary evaporator. The dark oil was purified by Kugelrohr distillation to give a colorless oil (74.5 mg, 0.33 mmol) in 31 % yield.

Hex-5-enal (24).[25]

Method I

To a suspension of PCC/Al_2O_3 (100 g, 100 mmol) in DCM (340 mL) was added commercially available hex-5-en-1-ol (5.0 g, 50 mmol) neat. The mixture was stirred overnight at RT. The reaction mixture was then filtered through a pad of silica gel (15 g) and washed with Et_2O and concentrated on a rotary evaporator with a 10 °C water bath. The next reaction was carried out without further purification.

Hept-6-en-2-ol (25).[25]

To crude aldehyde **24** (4.9 g, 50 mmol) in Et_2O (57 mL) at –20 °C was added methyl magnesium bromide (3.0M in THF, 16.7 mL, 50 mmol) dropwise. The reaction mixture was then warmed to RT, stirred for 10 min, cooled back down to –20 °C, and then quenched with aqueous NH_4Cl solution (45 mL). The mixture was diluted with Et_2O (100 mL) and the aqueous phase was extracted with Et_2O (2 x 57 mL). The combined organic layers were dried over $MgSO_4$ and concentrated on a rotary evaporator. The next reaction was carried out without further purification.

6-Iodohept-1-ene (7).[25]

To the 0 °C yellow mixture of triphenylphosphine (26.23 g, 100 mmol), imidazole (6.81 g, 100 mmol) and iodine (25.38 g, 100 mmol) in DCM (1000 mL) was added a solution of crude alcohol **25** (5.71 g, 50 mmol) in DCM (55 mL). The rest of the reaction was carried out a described for **6**. The dark oil was purified by Kugelrohr distillation to give a colorless oil (4.11 g, 20 mmol) in 39% over three steps.

Hex-5-enal (24).[25]

Method II

To a suspension of PCC (25.86 g, 120 mmol) in DCM (240 mL) was added commercially available hex-5-en-1-ol (4.8 mL, 40 mmol) neat. The mixture was stirred overnight at RT. The reaction mixture was then diluted with Et_2O and filtered through a pad of fluorsil (15 g). The remaining residue was triturated with Et_2O, filtered and concentrated on a rotary evaporator with a 10 °C water bath. Purification was carried out via column chromatography (10:1 pentane:Et_2O) to yield a slightly yellow oil (1.01 g, 10.3 mmol) in 26 %.

Dec-9-en-5-ol (26).[25]

To a –20 °C solution of **24** (1.01 g, 10.3 mmol) in THF (5.5 mL) was added butylmagnesium chloride (2.1 M in THF, 9.8 mL, 20.6 mmol) dropwise. The reaction mixture was allowed to stir for 20 min at –20 °C and then was diluted with Et_2O and quenched with NH_4Cl. The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was carried on column chromatography (6:1 pentane:Et_2O) to produce a pale yellow oil (0.61 g, 3.9 mmol) in 38% yield.

6-Iododec-1-ene (8).[25]

A solution of alcohol **26** (0.61 g, 3.9 mmol) in DCM (5 mL) was added to a premixed solution of triphenylphosphine (2.2 g, 8.4 mmol), imidazole (0.57 g, 8.4 mmol) and iodine (2.13 g, 8.4 mmol) in DCM (85 mL) that was prepared as described for **1**. The reaction was carried as described for **1**. The dark oil obtained was purified by Kugelrohr distillation to give a colorless oil (0.16 g, 0.6 mmol) in 14% yield.

1-(Iodomethyl)-2-methylcyclopentane (13).[25]

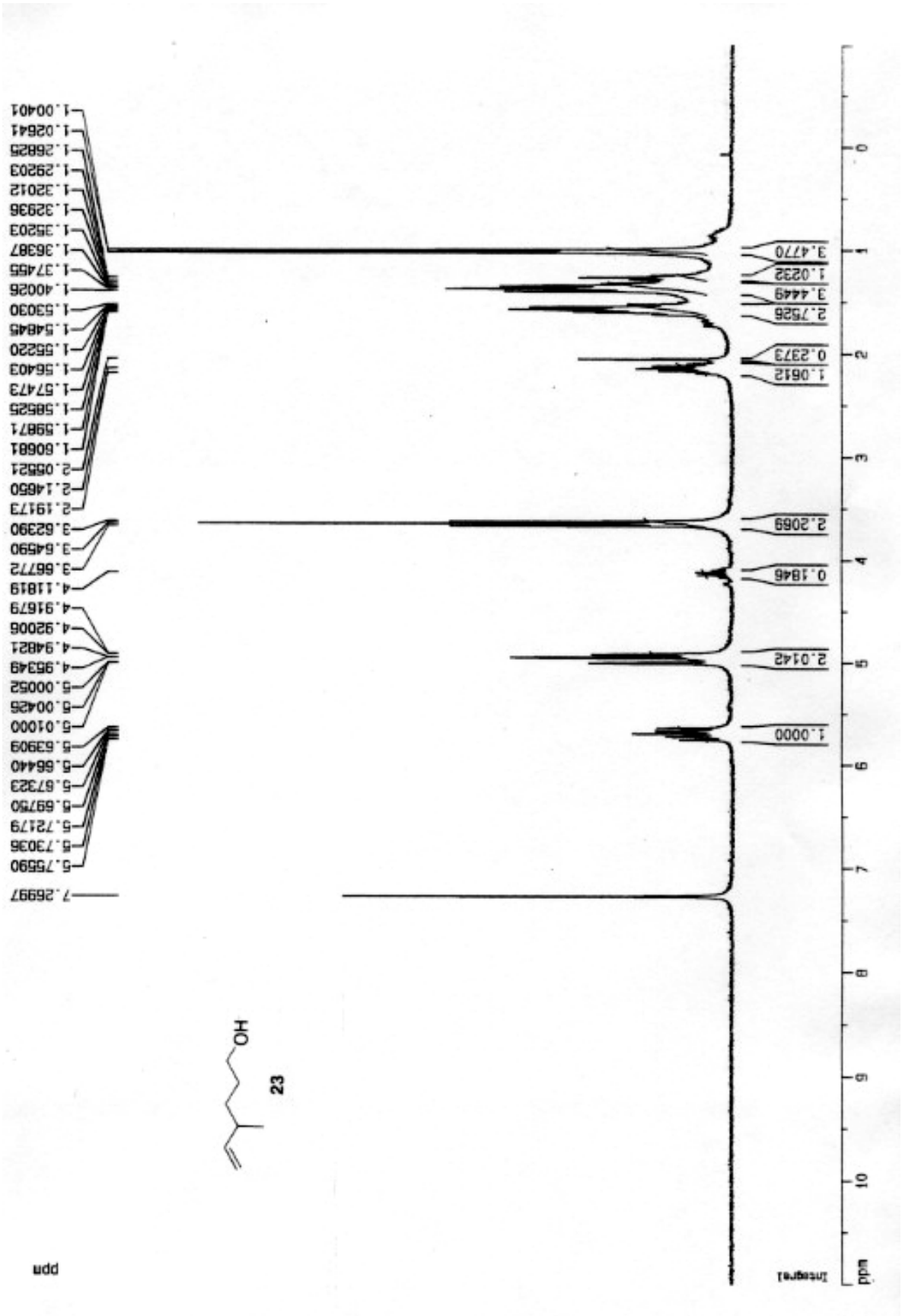
A 0.3 M solution of either **6** or **7** was cyclized according to the procedure described above with 10 % bis(tributyltin) as the radical initiator. Aliquots of 100 μL were removed at various times and analyzed via a gas chromatograph.

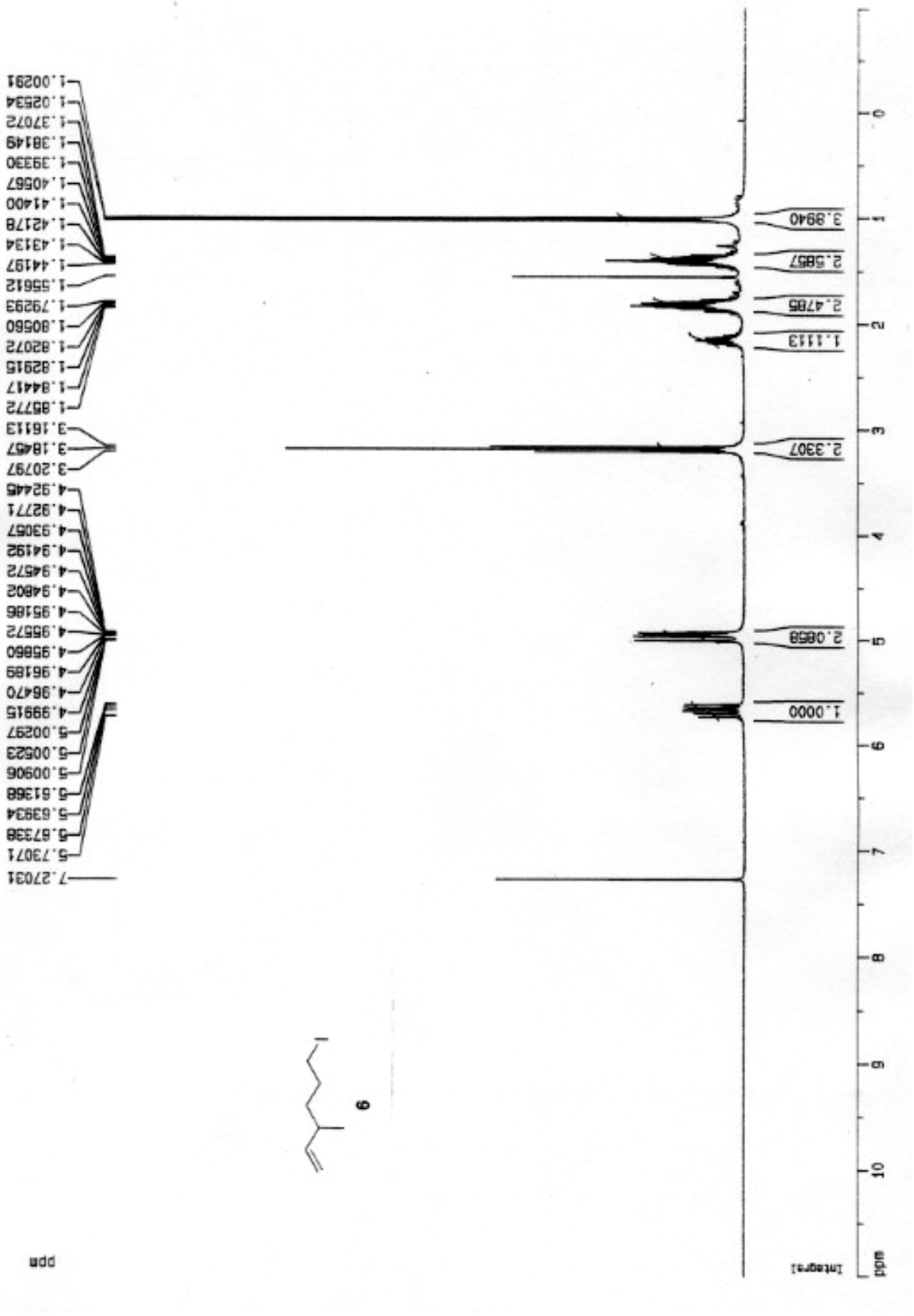
1-Butyl-2-(iodomethyl)cyclopentane (14).[25]

A 0.3 M solution of **8** was cyclized using 10% bis(tributyltin) as described earlier. Aliquots of 100 μL were removed at various times and analyzed via gas chromatograph.

APPENDIX A

^{1}H NMR SPECTRA OF INTERMEDIATES, PRECURSORS AND CYCLIZED PRODUCTS


OH
23
ppm
Integral


ppm
Integral
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2.5857
2.4785
1.1113
2.3307
2.0858
1.0000
7.270311
5.730711
5.673381
5.639341
5.613681
5.009061
5.005231
5.002971
4.999151
4.964701
4.961891
4.958601
4.955721
4.951861
4.948021
4.945721
4.941921
4.930571
4.927711
4.924451
3.207971
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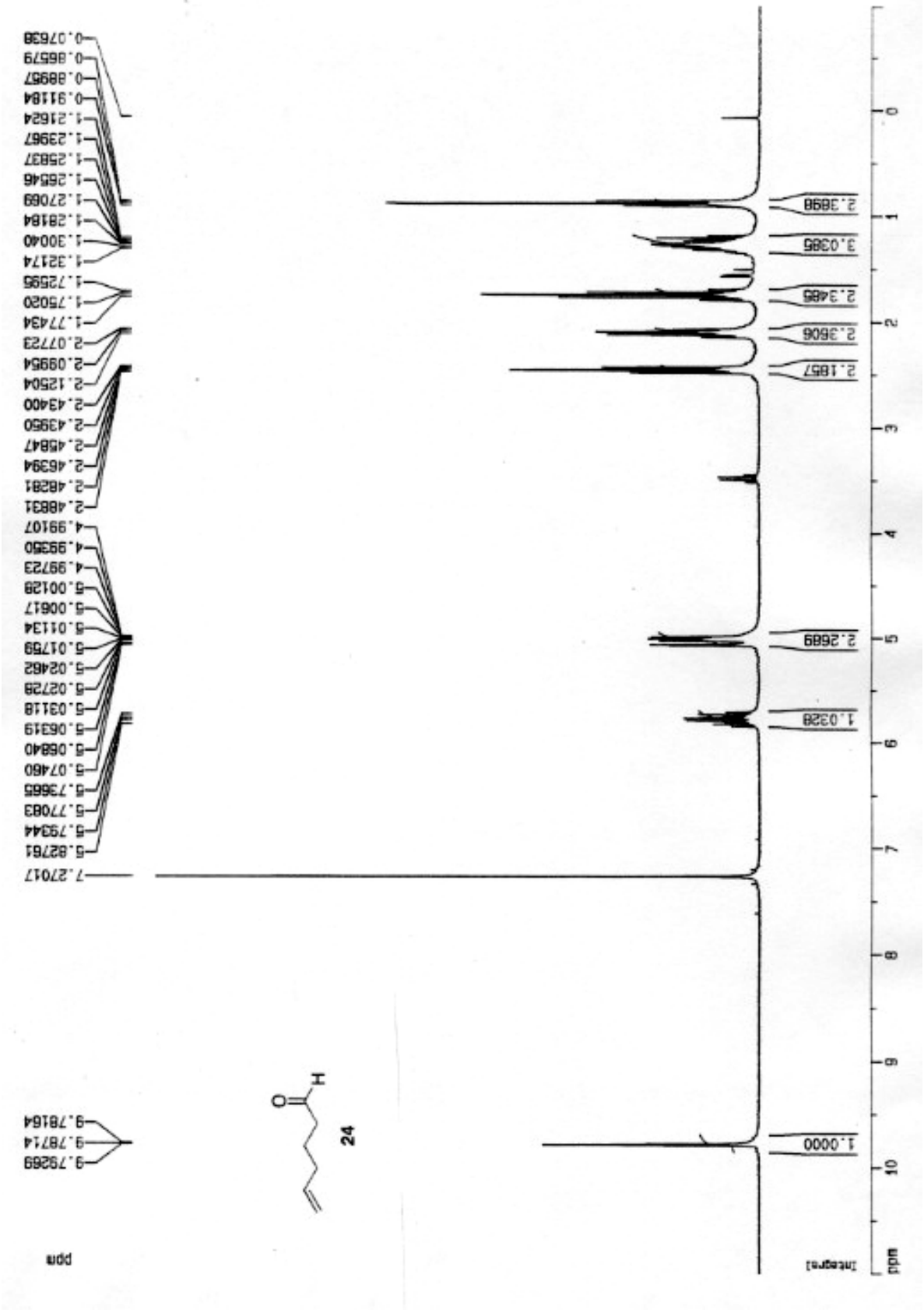
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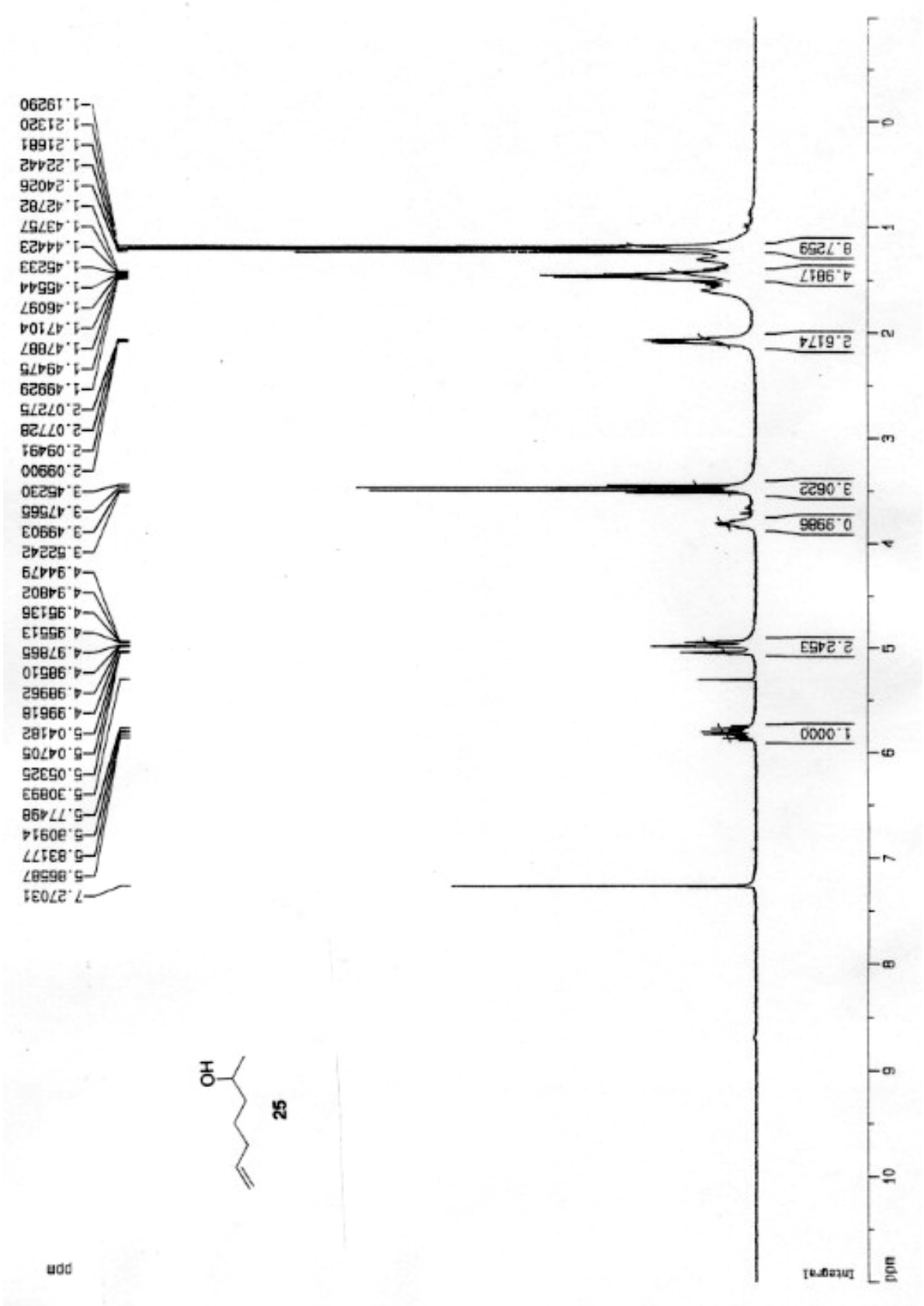
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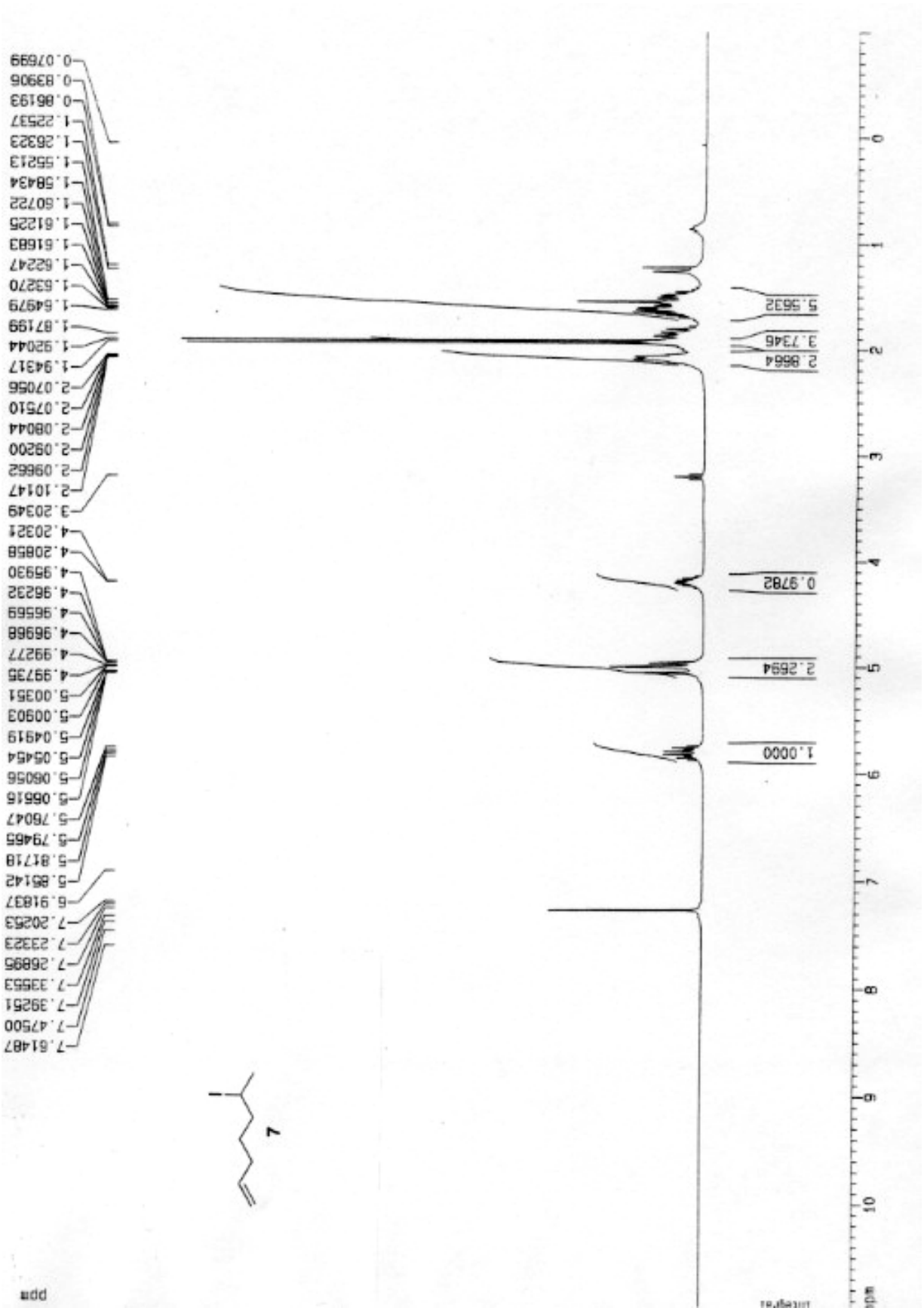
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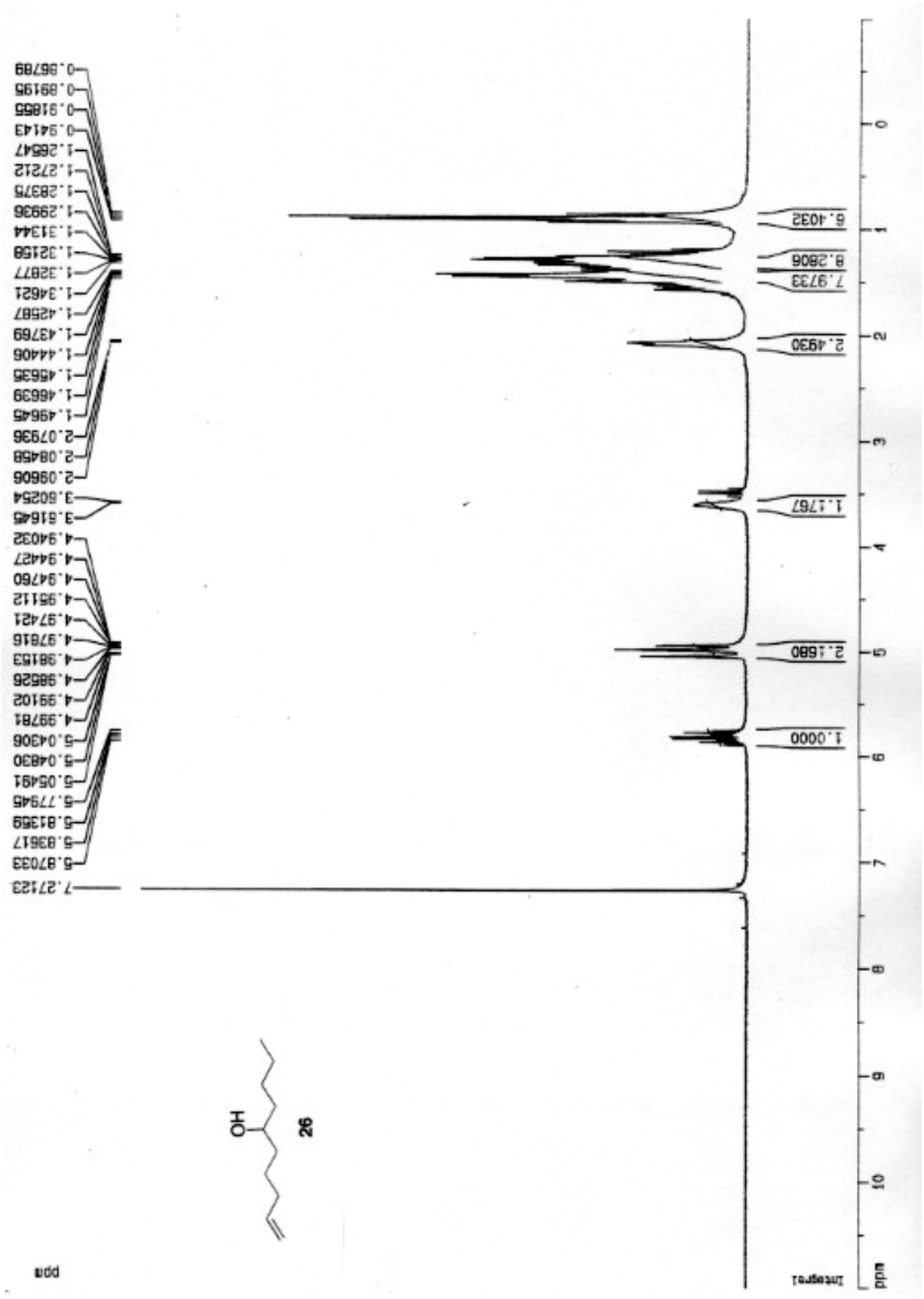
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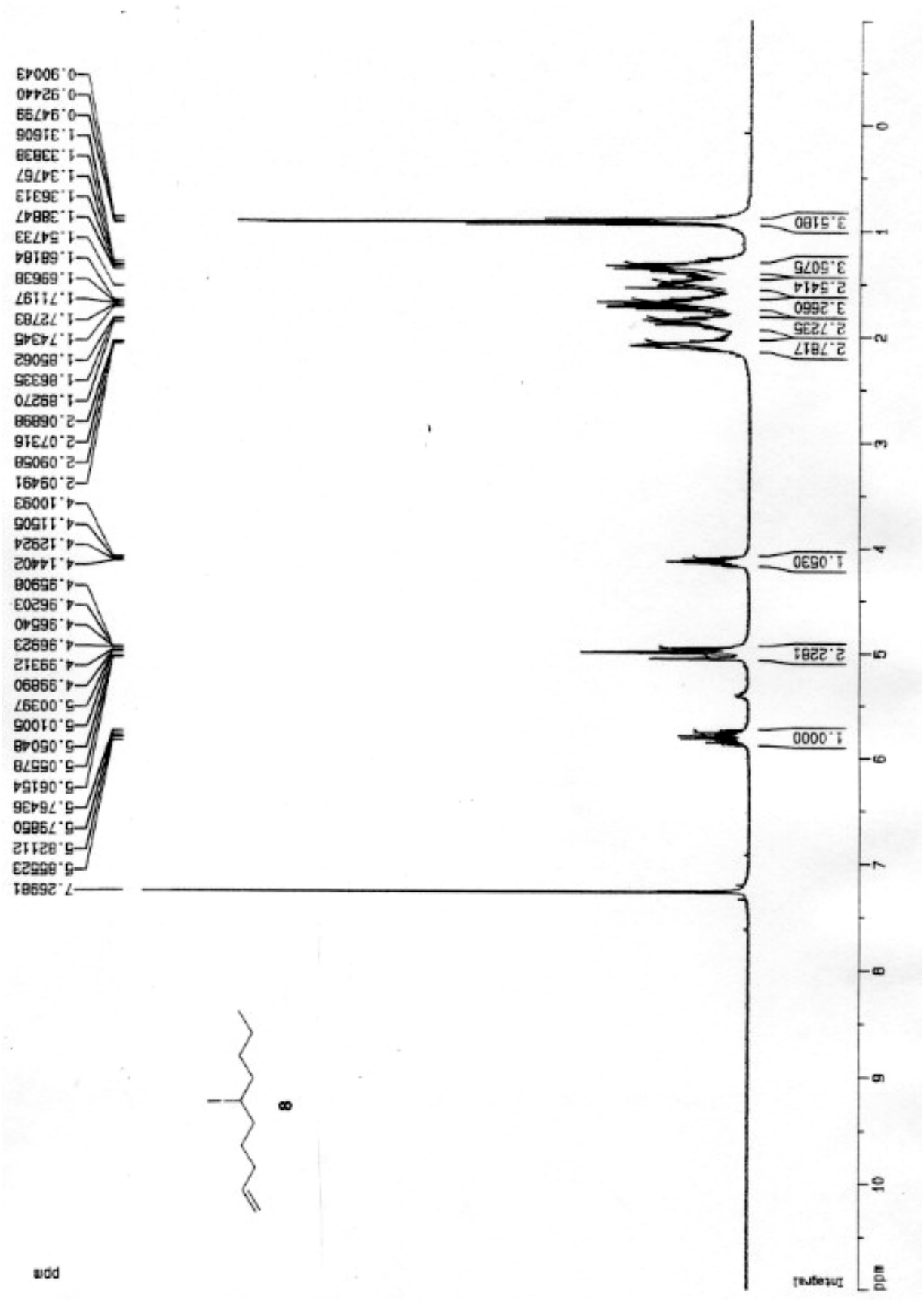
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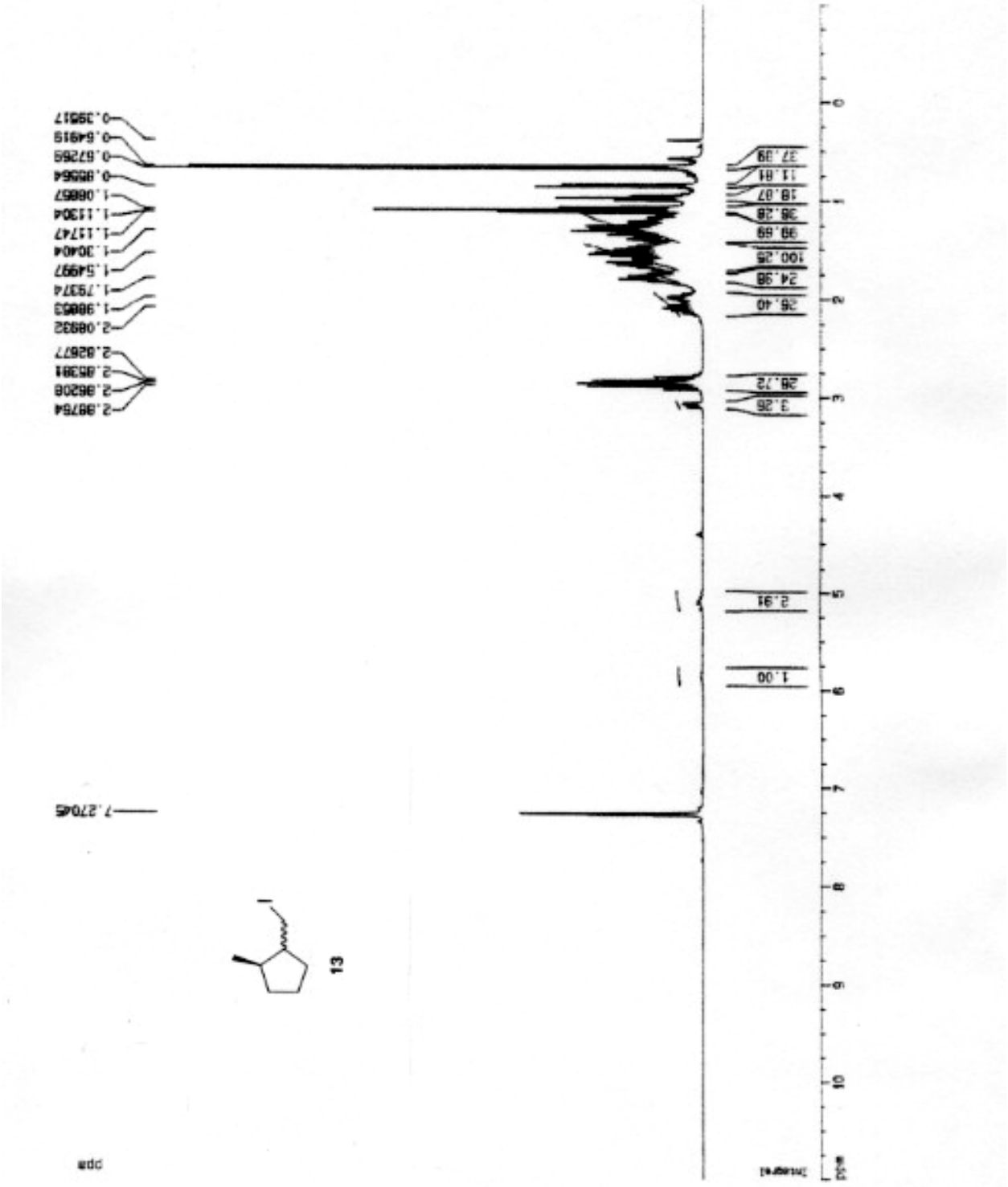
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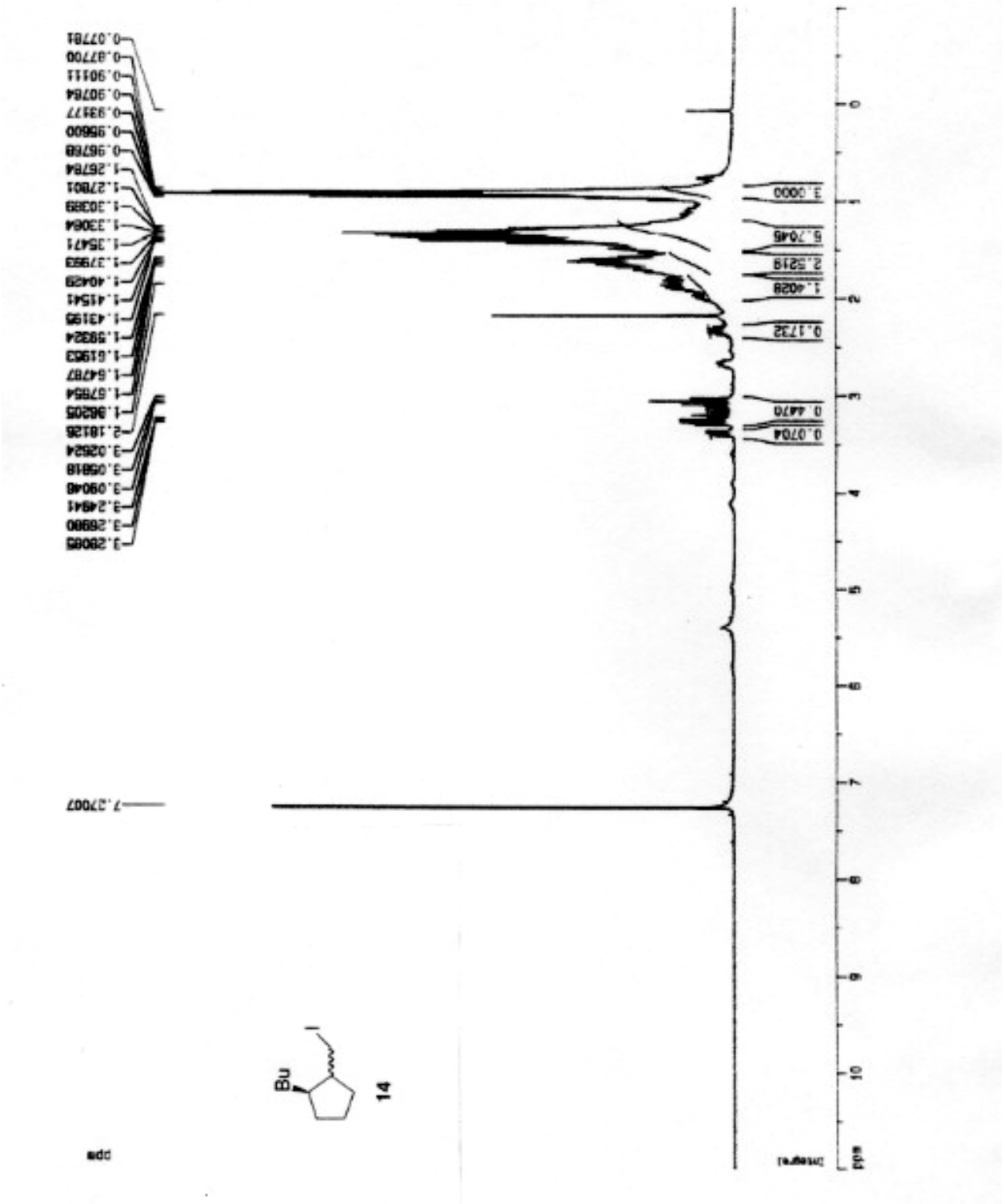
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14
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APPENDIX B

GAS CHROMATOGRAMS OF STANDARDS AND CYCLIZED PRODUCTS

GC PARAMETERS

Column: HP-1 capillary methyl siloxane column of 30 m in length and 0.32 mm in diameter with a 0.25 μm film

Initial Temp: 40 °C

Ramp1 Temp: 10 °C/min until 150 °C; hold 10 min

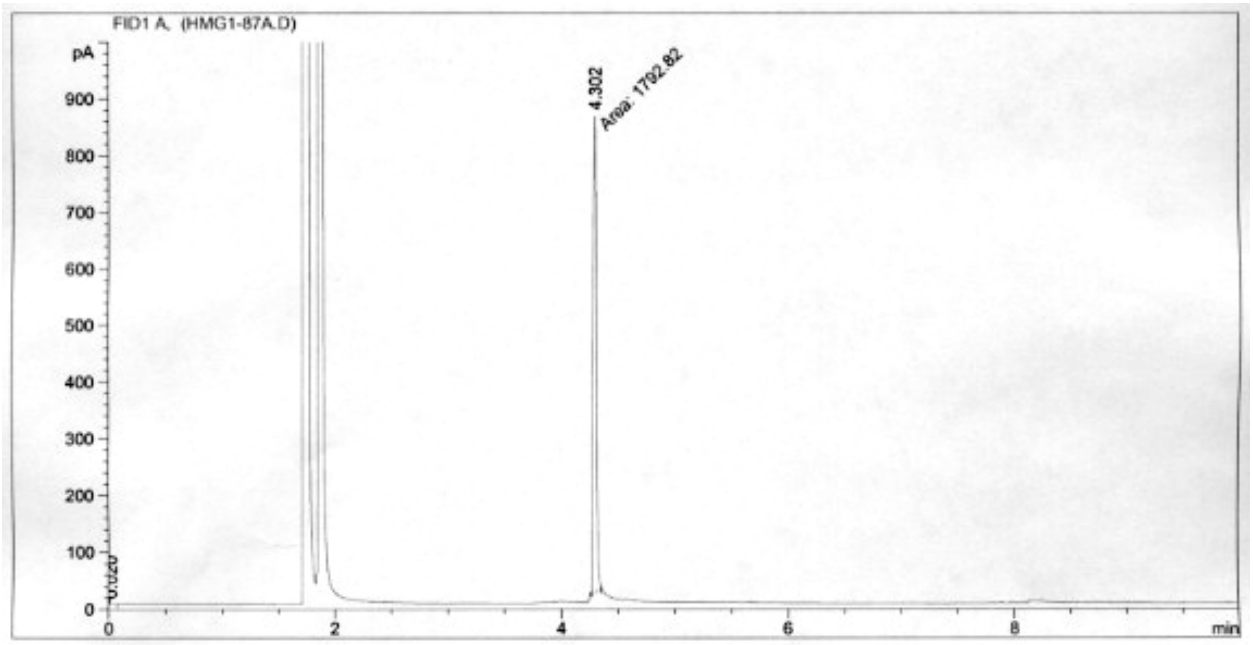
Ramp2 Temp: 20 °C/min until 300 °C; hold 5 min

Final Temp: 300 °C

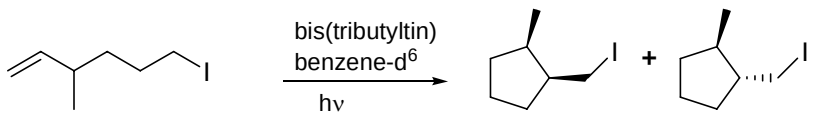
Detector: FID

Gas Flow Rate: 32 cm/s

6-iodo-3-methylhexene **6** standard for LEFT GC column

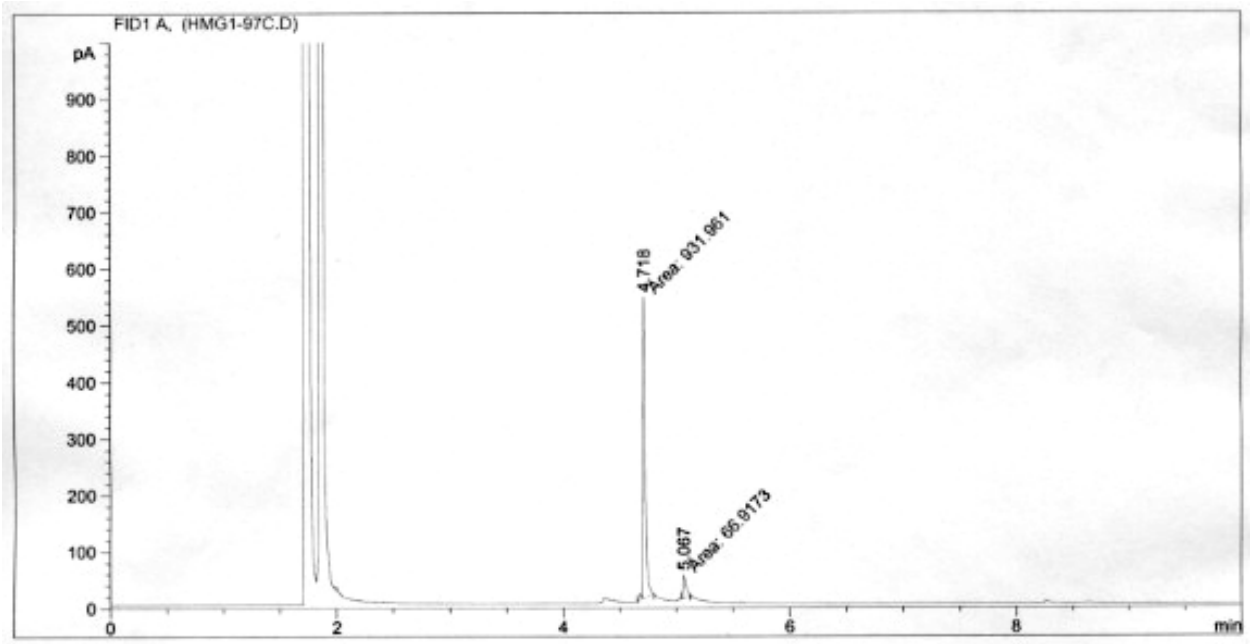


Atom transfer cyclization at 5 °C for 270 min

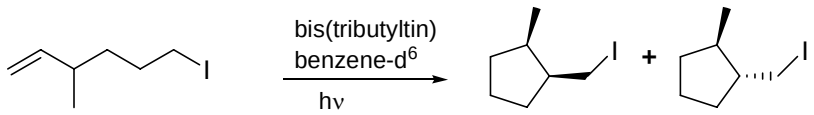


6 **13a** **13b**

13a:13b = 1:13.3

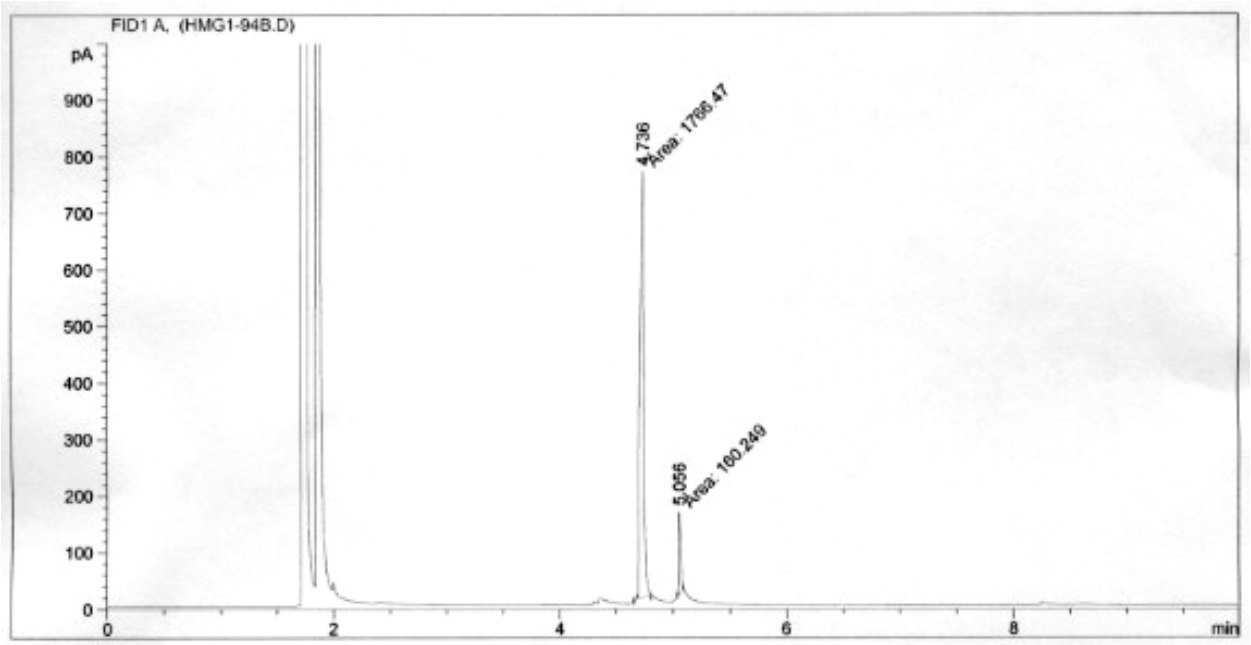


Atom transfer cyclization at 15 °C for 210 min

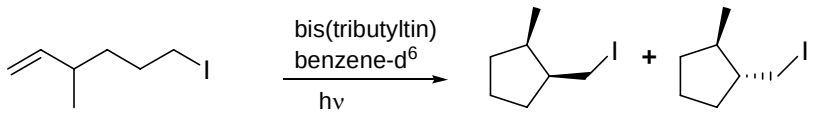


6 **13a** **13b**

13a:13b = 1:11.5

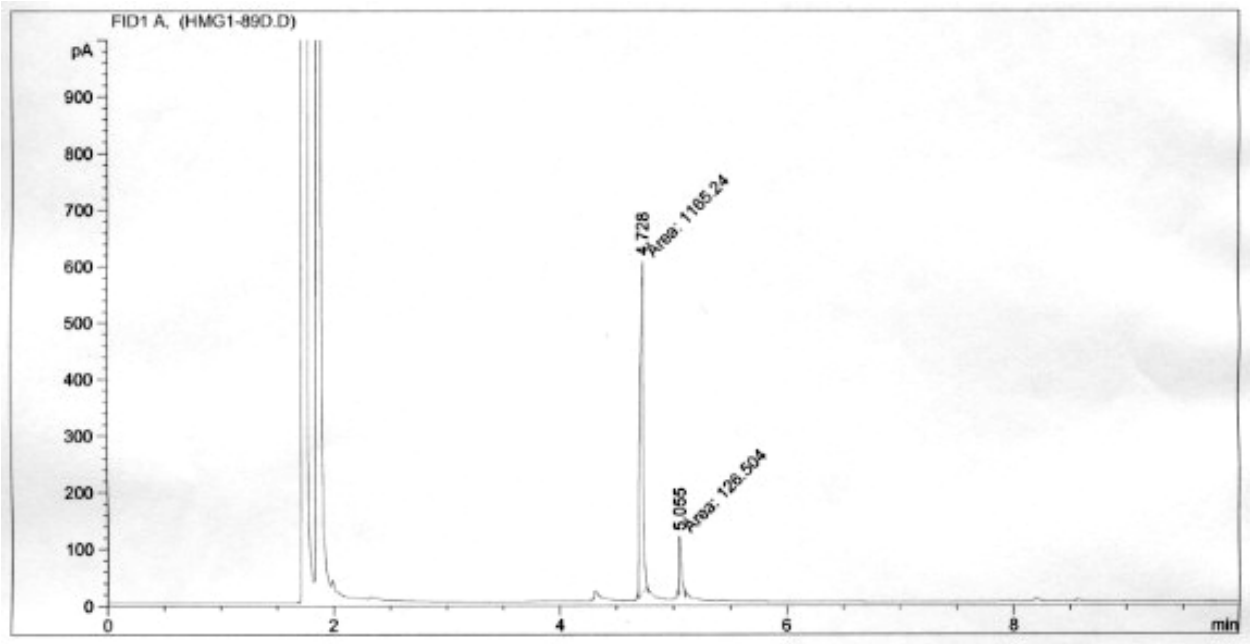


Atom transfer cyclization at 25 °C for 150 min

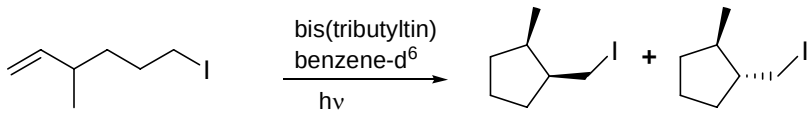


6 **13a** **13b**

13a:13b = 1:9.0

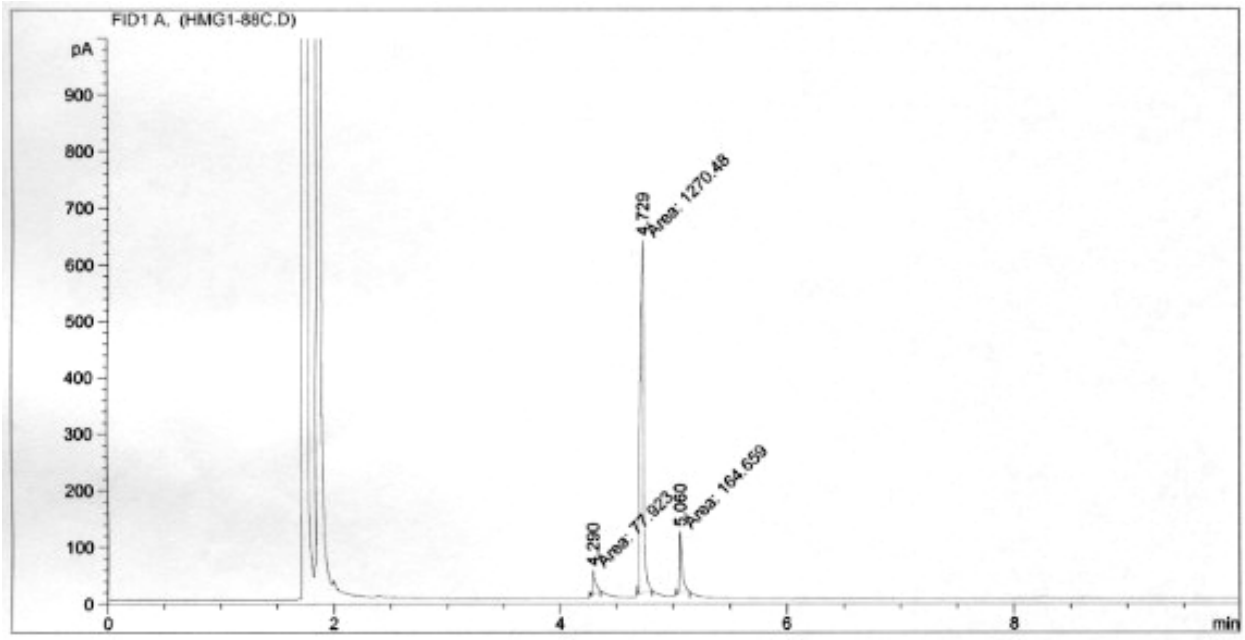


Atom transfer cyclization at 35 °C for 120 min

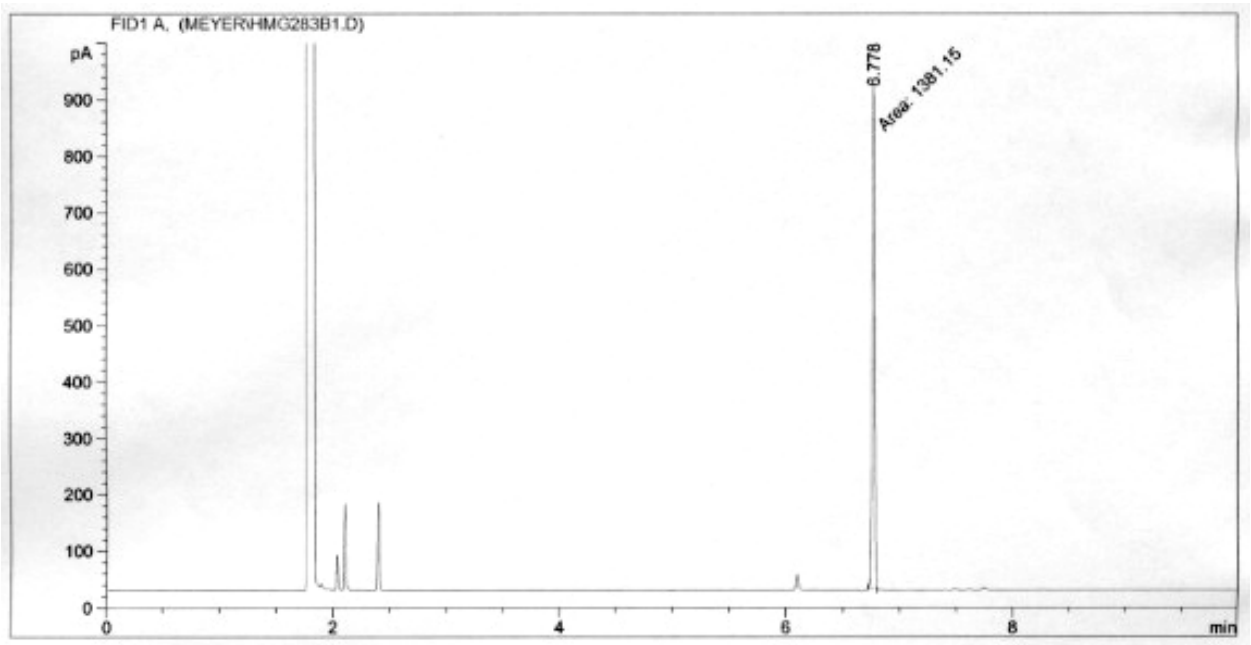


6 **13a** **13b**

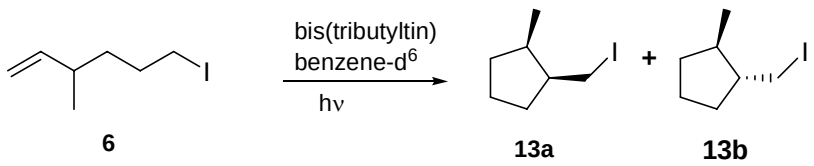
13a:13b = 1:7.0



6-iodo-3-methylhexene **6** standard for RIGHT GC column

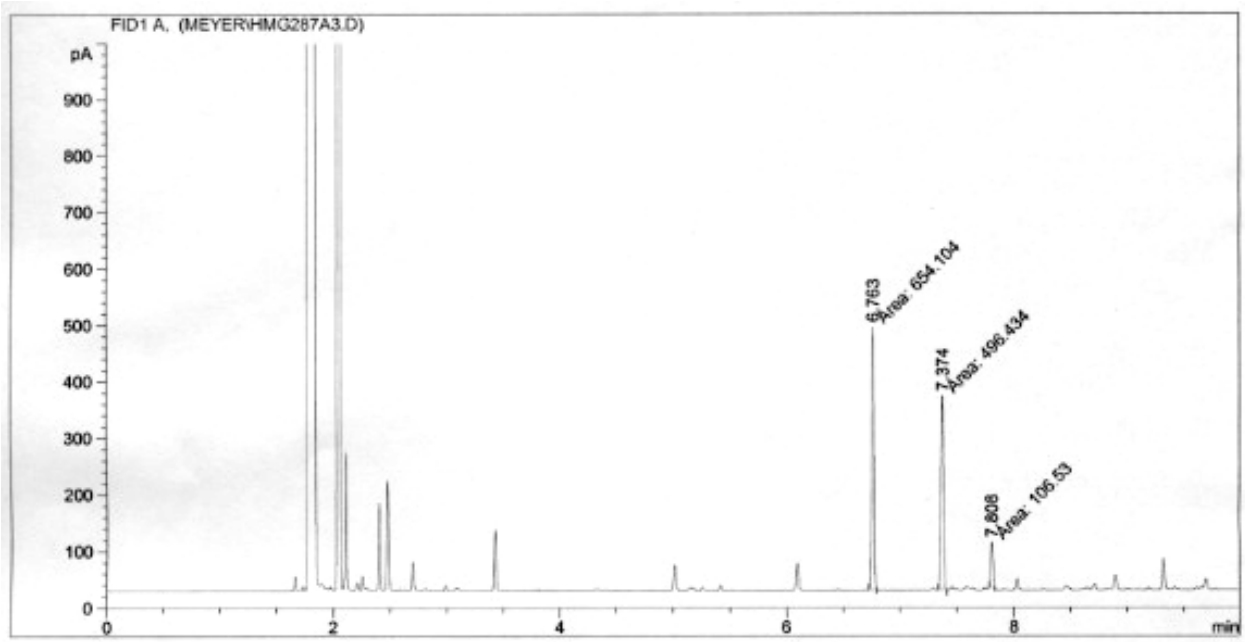


Atom transfer cyclization at 80 °C for 240 min

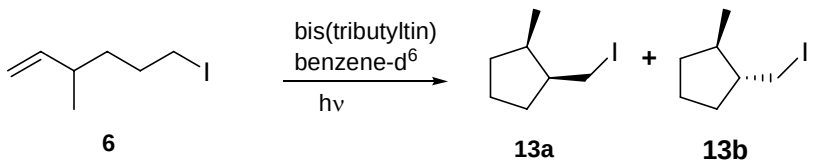


6 **13a** **13b**

13a:13b = 1:4.5

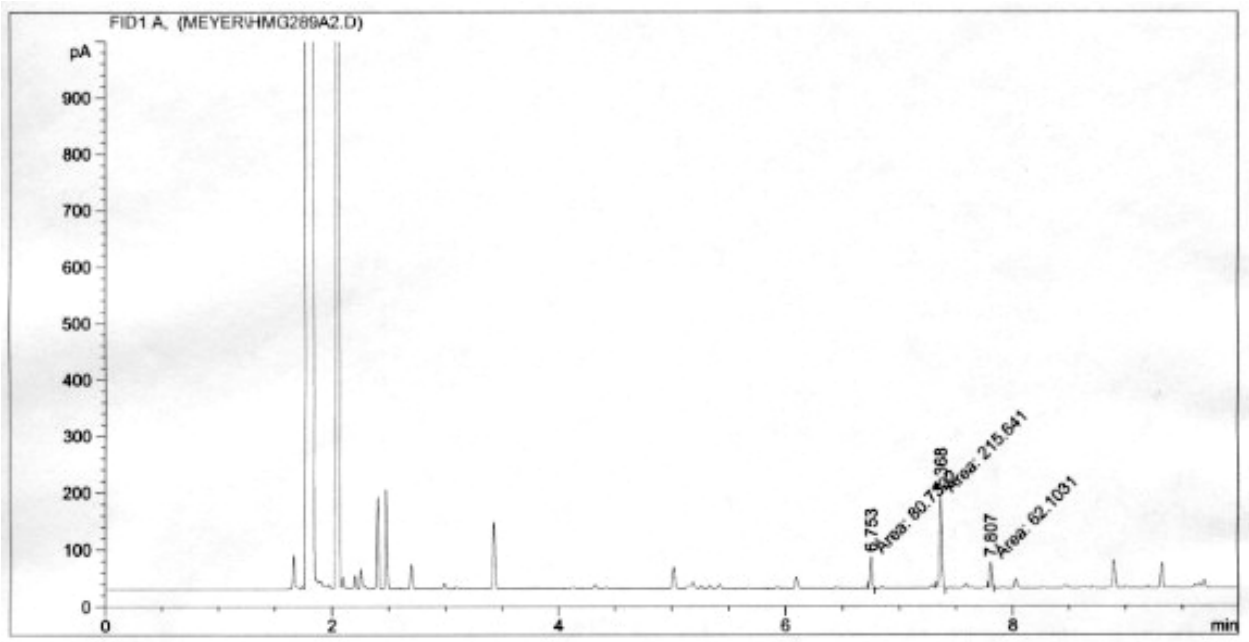


Atom transfer cyclization at 80 °C for 300 min

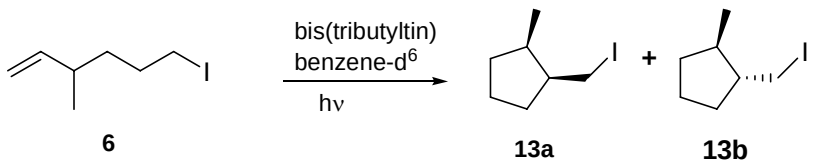


6 **13a** **13b**

13a:13b = 1:3.5

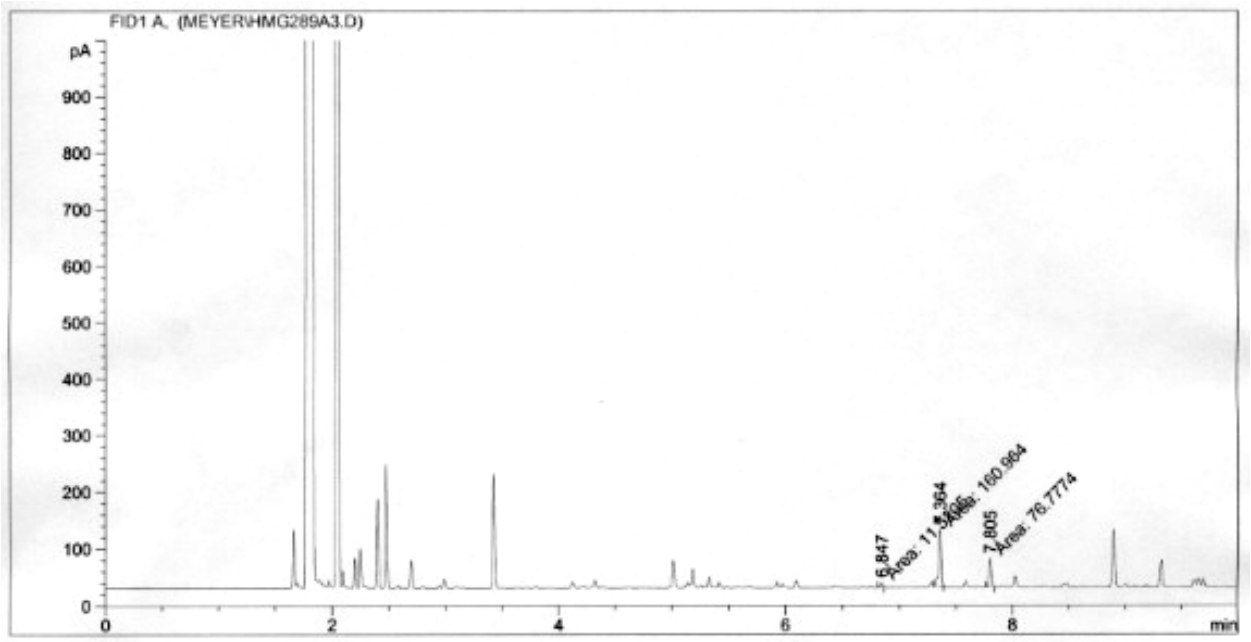


Atom transfer cyclization at 80 °C for 420 min

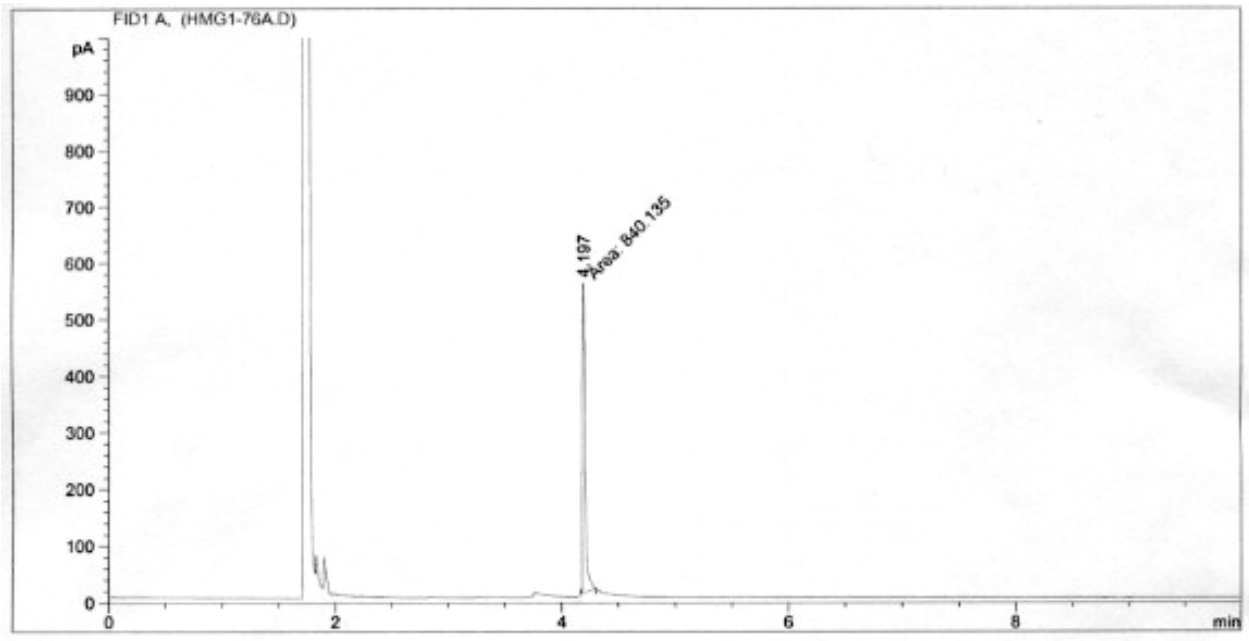


6 **13a** **13b**

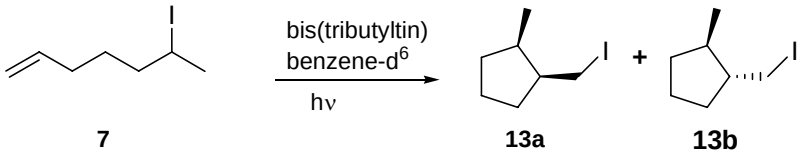
13a:13b = 1:2.0



6-iodoheptene **7** standard

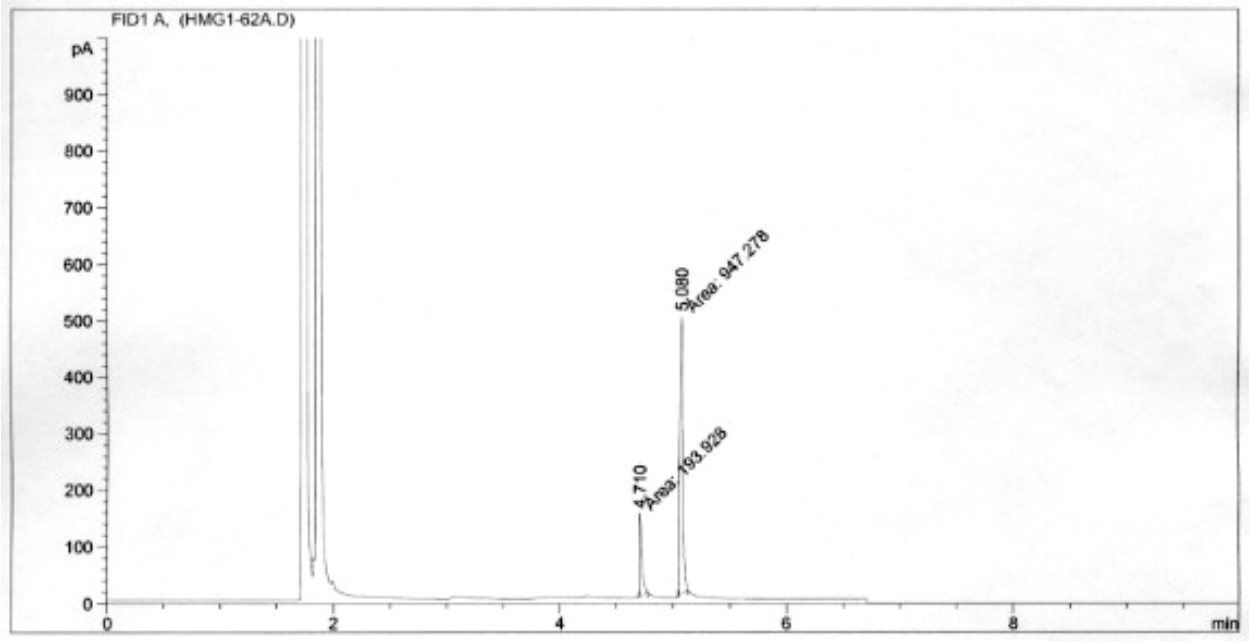


Atom transfer cyclization at 5 °C for 90 min

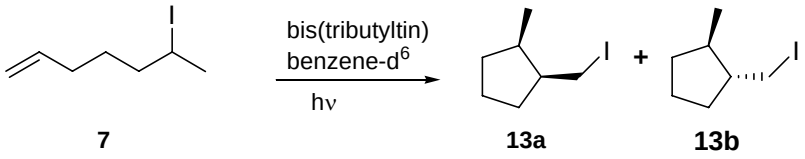


7 **13a** **13b**

13a:13b = 4.9: 1

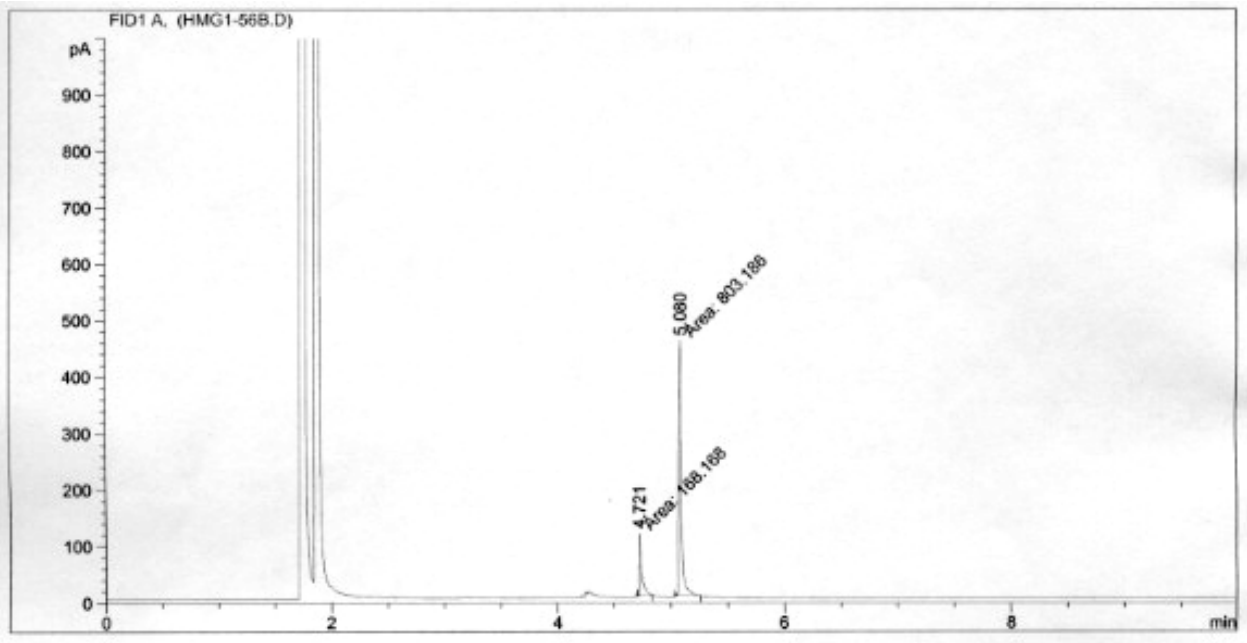


Atom transfer cyclization at 15 °C for 75 min

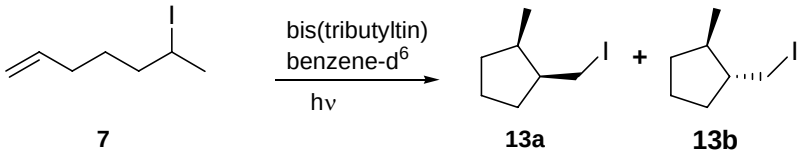


7 **13a** **13b**

13a:13b = 4.8: 1

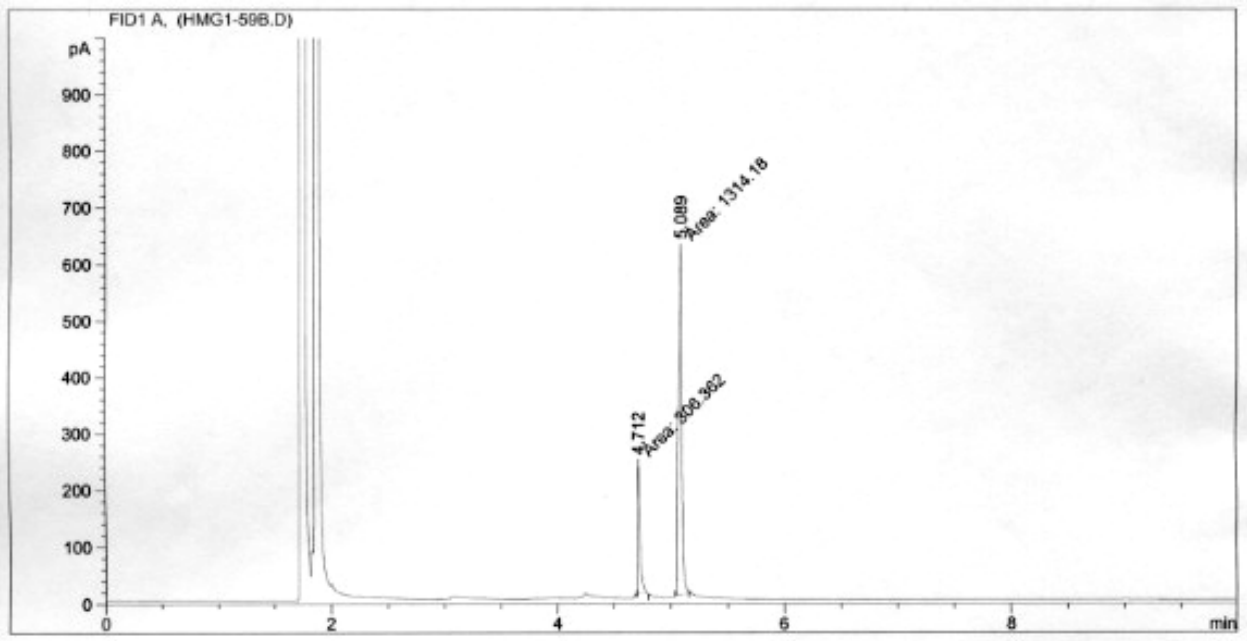


Atom transfer cyclization at 25 °C for 45 min

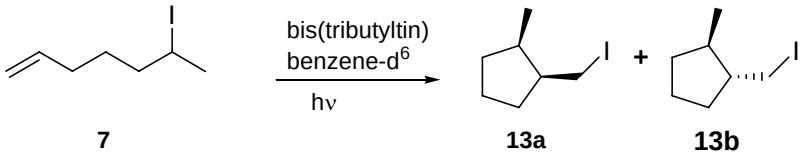


7 **13a** **13b**

13a:13b = 4.3: 1

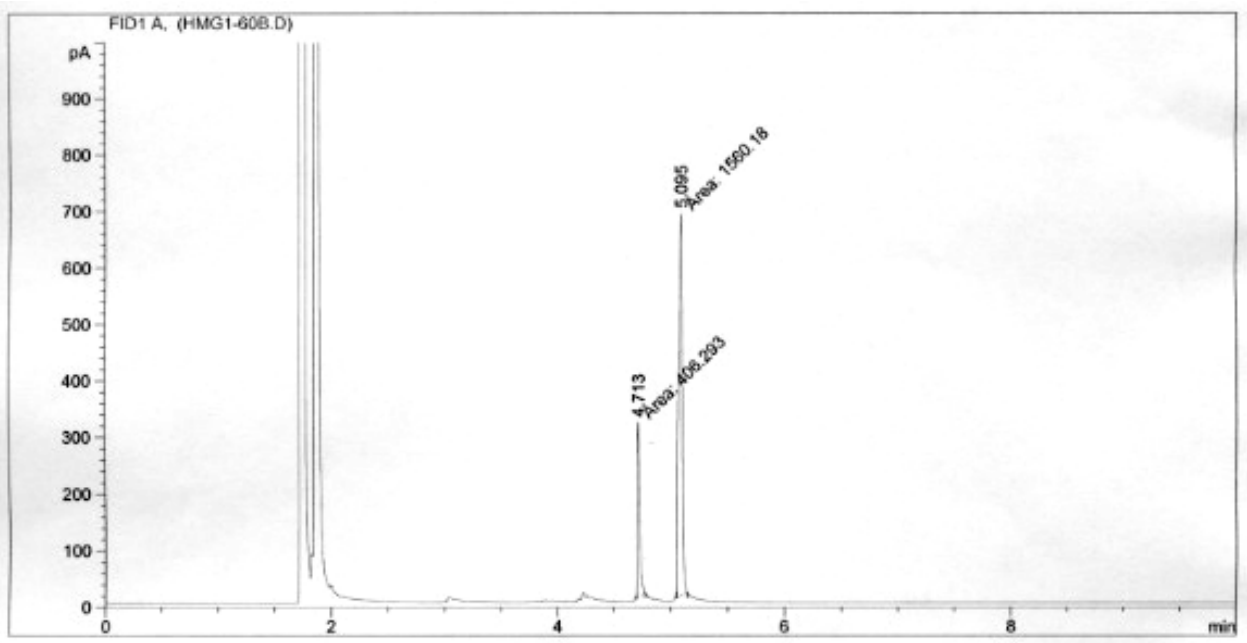


Atom transfer cyclization at 35 °C for 45 min

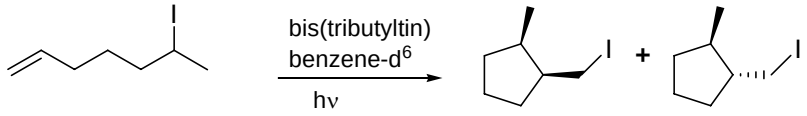


7 **13a** **13b**

13a:13b = 3.8: 1

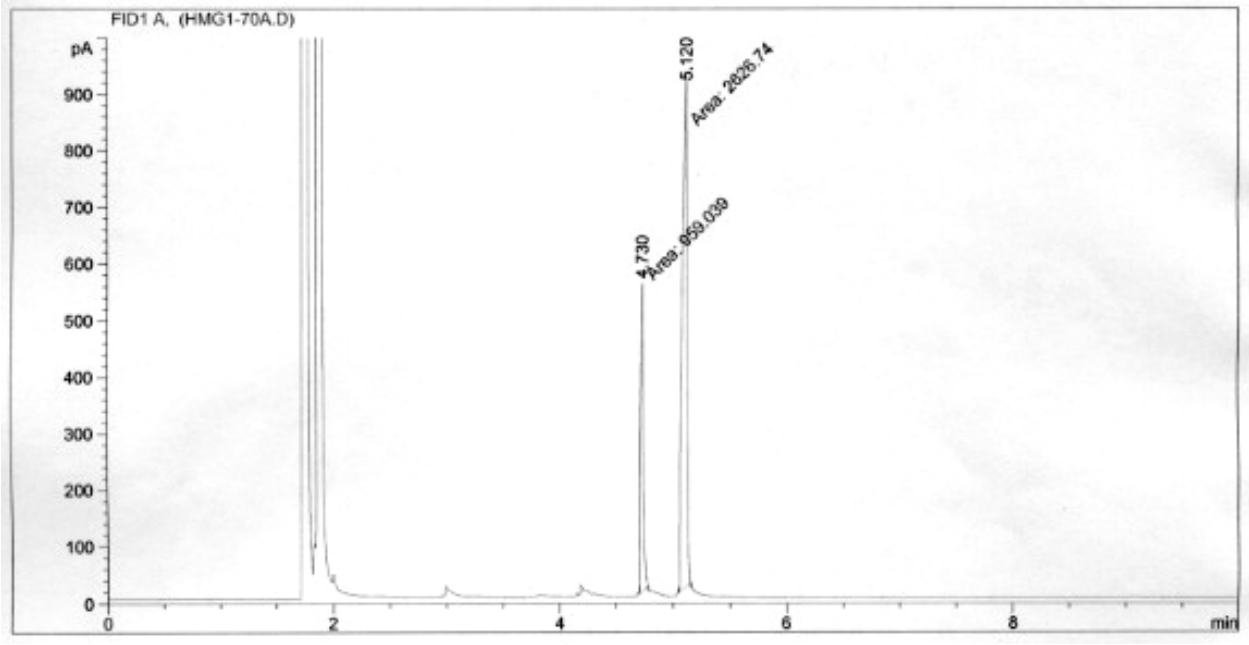


Atom transfer cyclization at 80 °C for 90 min

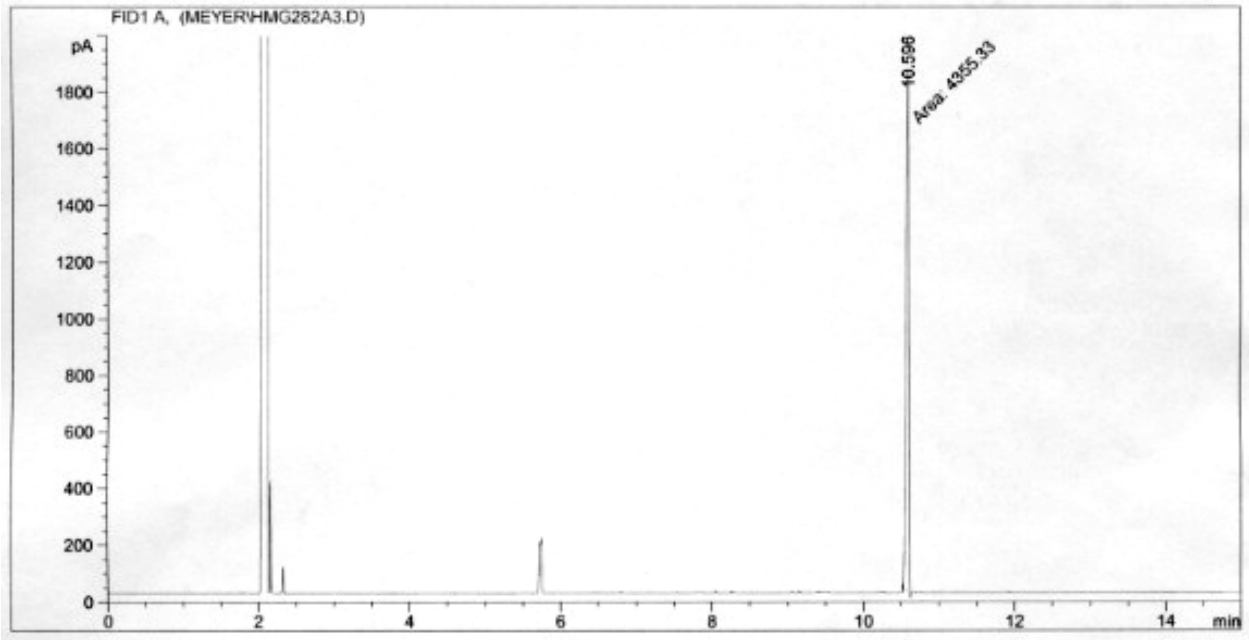


7 **13a** **13b**

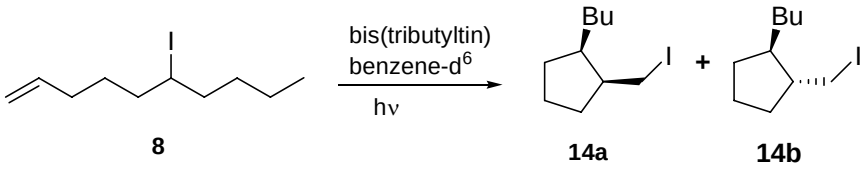
13a:13b = 2.7: 1



6-iododecene **8** standard

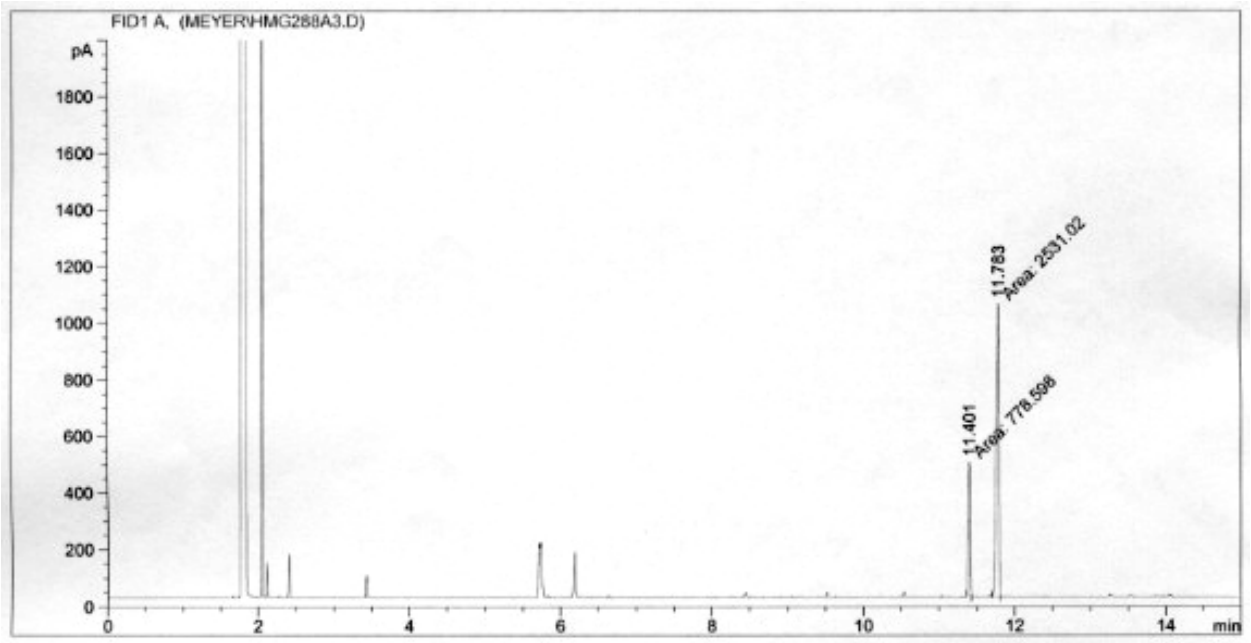


Atom transfer cyclization at 5 °C for 120 min

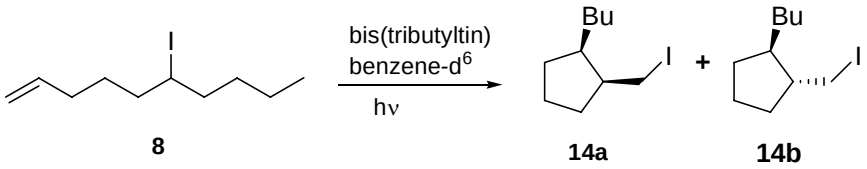


8 **14a** **14b**

14a:14b = 3.2:1

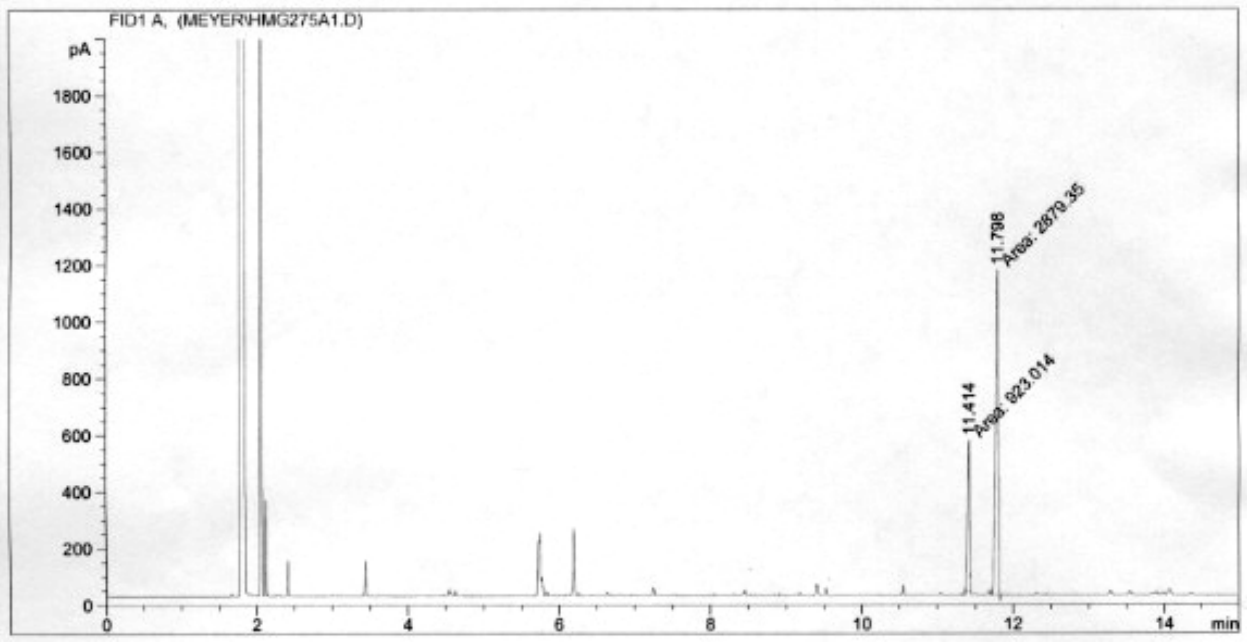


Atom transfer cyclization at 20 °C for 150 min

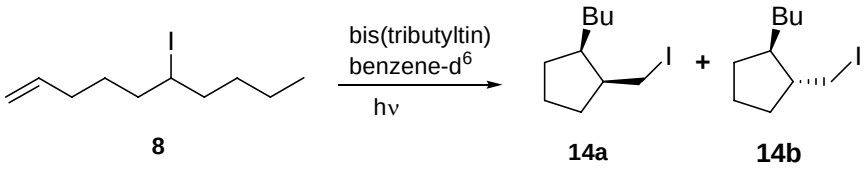


8 **14a** **14b**

14a:14b = 3.1:1

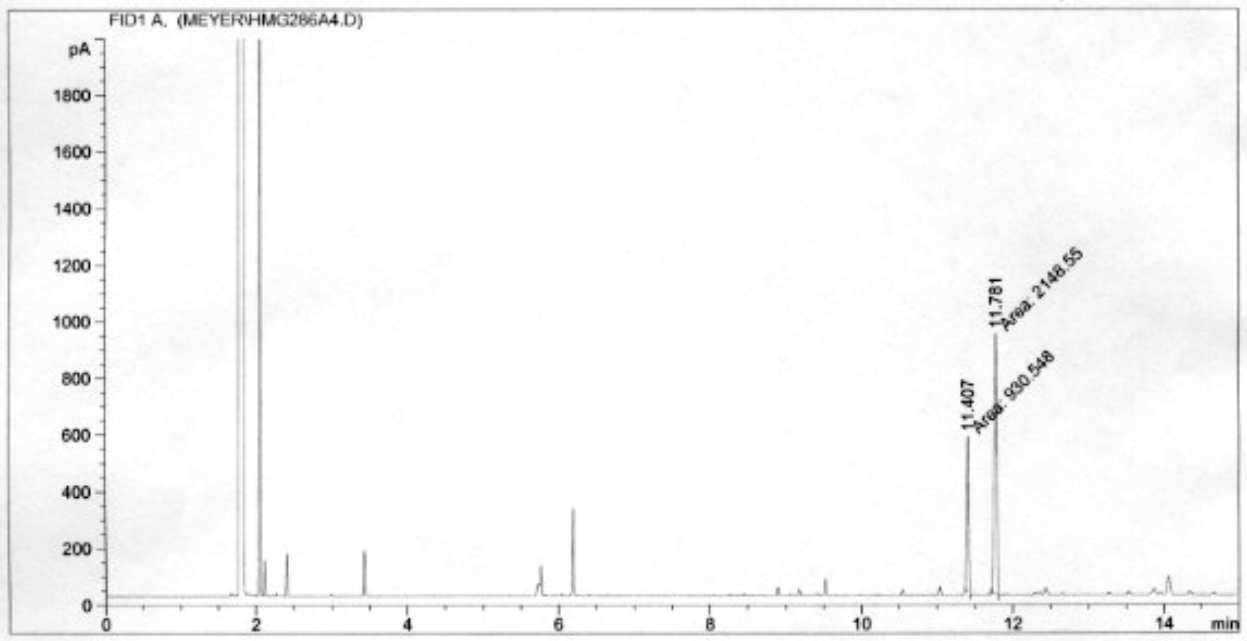


Atom transfer cyclization at 80 °C for 180 min



8 **14a** **14b**

14a:14b = 2.3:1



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