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Investigating Ring Closing Metathesis Product Favorability by Varying the Alkyne Substituent on a Dienyne

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Investigating Ring Closing Metathesis Product Favorability by Varying the Alkyne Substituent on a Dienyne

A Thesis

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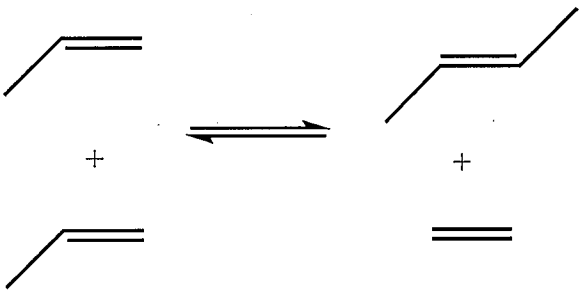
Abbreviations and Definitions

Alkene, Olefin	double bond
Alkylidene, Metal-carbene	A carbon (with substituents) that has a double bond with a metal.
Bu	butyl group
Cy	cyclohexane
d	doublet
DCM	dichloromethane
dd	doublet of doublets
Diene	a compound which possesses two double bonds
Dienyne	a compound which possesses two double bonds and a triple bond
Enyne	a compound which possesses a double bond and a triple bond
M	metal
m	multiplet
MHz	megahertz
mmol	millimole
PCC	pyridinium chlorochromate
Ph	phenyl group
RCM	ring closing metathesis
t	triplet
q	quartet

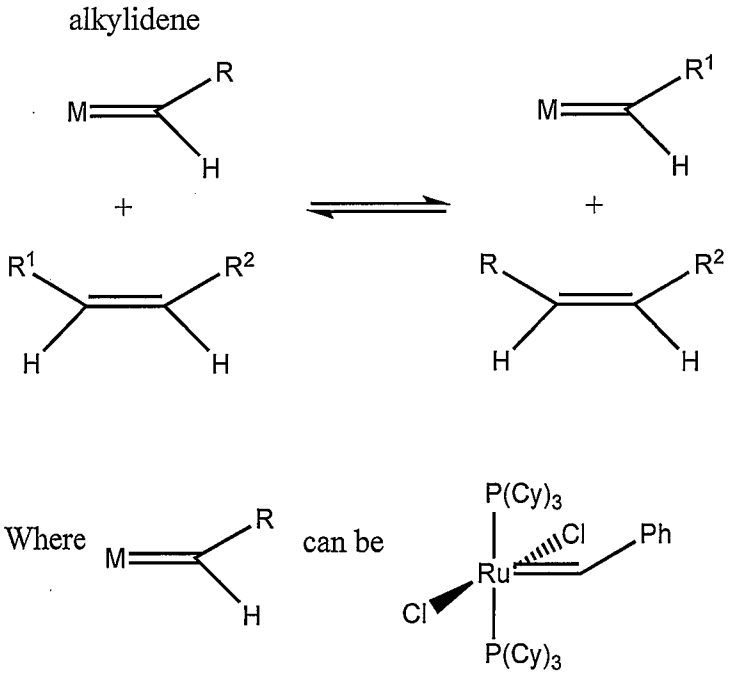
Introduction

Diene metathesis, which is also known as an olefin metathesis, has been very important for the development of synthetic strategies in organic chemistry since it's inception in the 1950s. The olefin metathesis reaction is when two alkenes exchange the carbons on their double bonds, thus producing two new carbon□carbon double bonds.[1] An example of this basic reaction can be seen in Scheme 1, where a common use for this reaction is in the preparation of ethylene and 2-butene from propylene in industry.[2]



Scheme 1. A generic olefin metathesis reaction where propylene is used to produce ethylene and 2-butene.

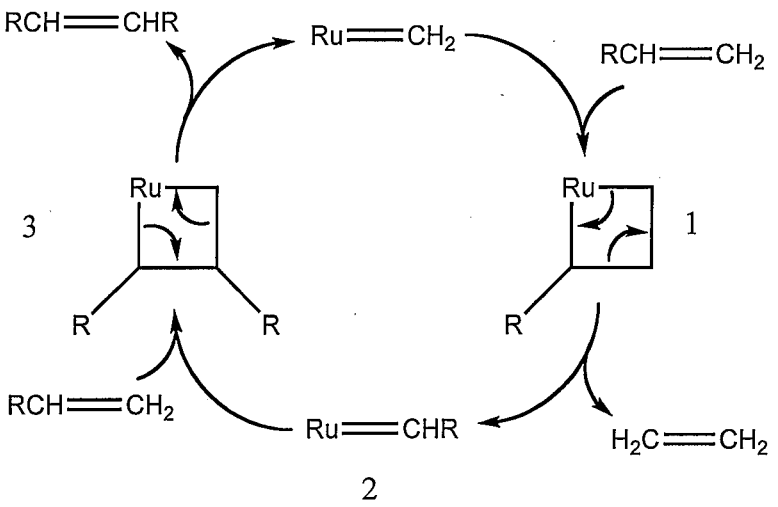
The olefin metathesis is done through a metal catalyst, which will contain metals such as tungsten, molybdenum, or ruthenium. A commonly used catalyst is the ruthenium catalyst developed by R. Grubbs, for which he shared the Nobel Prize in Chemistry with R. Schrock in 2005, and this catalyst can be seen in Scheme 2. Because of the use of metal catalysts, the transfer of the carbon groups can be described as taking place between an alkylidene and alkene.[2] An alkylidene is a metal with a double bond to a carbon, and an example of one can be seen in Scheme 2, which shows a basic example of the reaction.



Grubbs first generation catalyst

Scheme 2. A generic alkylidene and alkene metathesis reaction, where the identity of the alkylidene can be Grubbs first generation catalyst, and Cy denotes a cyclohexane.

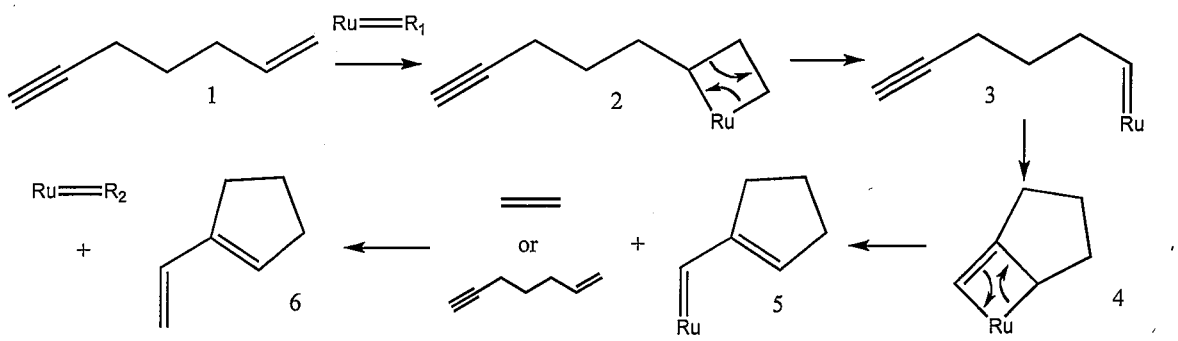
What is particularly notable about these metathesis reactions is that the metal complex is regenerated so it can be continued as a catalytic cycle. This is done through the formation of the metal-carbene, also known as an alkylidene, intermediates of the metathesis.[3] As seen in Scheme 3, the catalytic cycle proceeds with the catalyst forming a metallocyclobutane with an olefin in step 1. In step 2, the metallocyclobutane collapses to give a carbene and a new olefin. The carbene forms another metallocyclobutane with an olefin in step 3 before collapsing, which regenerates a catalytic species that can be reused for another cycle.



Scheme 3. The ruthenium catalytic cycle of olefin metathesis

The concepts of olefin metathesis are not limited to double bonds or intermolecular reactions. Metathesis can also occur between an alkyne and an alkene, and this application was first reported in 1985.[4] Additionally, when the alkyne and alkene are present on the same compound, an enyne, then intramolecular rather than intermolecular metathesis is favored. This is referred to as an enyne ring closing metathesis reaction, (RCM).[5]

The mechanism for a ring closing metathesis is reminiscent of intermolecular olefin metathesis. Typically, the catalyst will react first with the alkene to regenerate the carbene, and this reactive species will proceed to complete the ring closing metathesis with the alkyne. This mechanism has been discussed and is supported in literature.[6,7] A general outline of the mechanism can be seen in Scheme 4 with 1-hepten-6-yne used as an example.



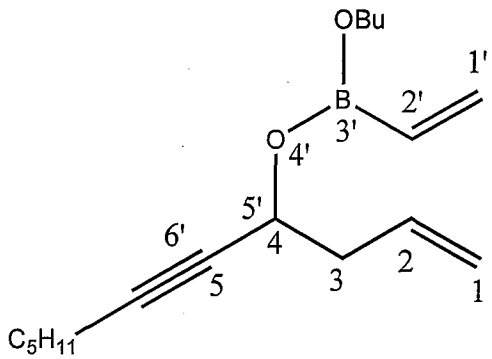
Scheme 4. A generic outline of the ene then yne metathesis reactions to undergo a ring closing metathesis with 1-hepten-6-yne.

In a similar manner to Scheme 3, Scheme 4 follows the catalytic cycle of ruthenium in order to undergo RCM. In Step 1, the catalyst forms a carbene with the double bond of the alkenyne. The metallocyclobutane of step 2 collapses to give a carbene in step 3. The carbene forms a metallocylcobutene with the triple bond and collapses in step 4 to give the compound in step 5, which still contains a carbene. If there is another double or triple bond available, with which to react, the carbene in step five can undergo further metathesis. In step 6, a new olefin was formed while the ruthenium proceeds to produce another carbene identity.

The size of the ring created is an important factor of ring closing metathesis. The shortest chain available for an enyne ring closing metathesis is a 1,6-enyne because it produces a five-membered ring. This is demonstrated in Scheme 4. A 1,5 enyne ring closing metathesis is not favorable due to the high energy and torsional constraints of making an unsaturated 4-membered ring. An example of this is how 1-undecen-5-yn-4-ol did not undergo metathesis in the presence of Grubbs first generation catalyst (unpublished work in McNulty lab)[8].

Heterocycles can be made through a ring closing metathesis with an enyne. Most of this work has been done with nitrogen and oxygen heterocycles.[9] An additional area of

interest involves the use of allylboronic esters with propargylic alcohols to produce cyclic allylboronic acids, and an example can be seen in Scheme 5.[10] In the previously mentioned 1-undecen-5-yn-4-ol, if the alcohol were replaced by an vinylic boronic ester, then a 1,6 ring closing metathesis would be possible, and this is shown in Scheme 5.



Scheme 5. The addition of an allylic boronic ester to 1-undecen-5-yn-4-ol makes a ring closing metathesis possible, and the products of this reaction can be seen in Scheme 6.

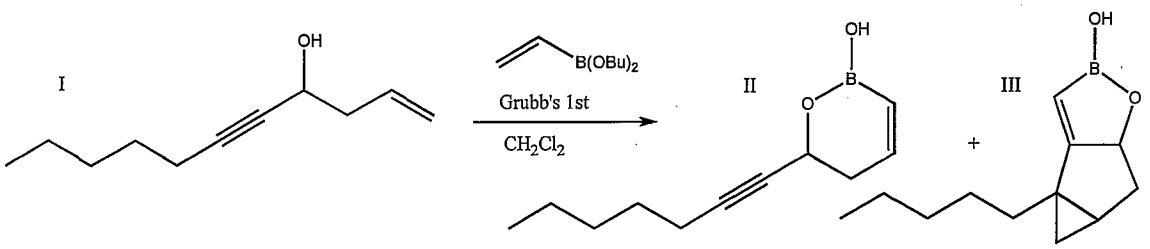
In a similar manner to compounds previously shown, the compound in Scheme 5 will undergo ring closing metathesis. Because there are three multiple bonds present, it is important to recall the carbene, which is present after the initial ring closing metathesis takes place. This carbene seen in step 5 of Scheme 4 has the potential to undergo an intermediate metathesis reaction. If an olefin is available on the cyclic structure in at least a 1,6 position, then the compound can undergo another intermediate reaction leading to at least a bicyclic species. This is referred to as tandem enyne metathesis.

Even though the first tandem enyne metathesis reactions were done primarily with terminal alkynes, there are instances in the literature where an internal alkyne can be used, provided that the internal alkyne is not sterically hindered.[11] In a similar manner to enyne metathesis, the alkene will react with the catalyst before the alkyne, as will the second alkene. However, an initially unexpected result of the tandem enyne metathesis of

several dienynes in the McNulty laboratory has shown that a cyclopropyl group could be formed under some conditions, and more information on this reaction can be found in the discussion of Figure 7.[12]

This work has explored the reactions of enynes with vinyl boronic acid dibutyl ester and Grubbs first generation catalyst. Of main interest is the tandem enyne metathesis of a dienyne compound. What makes this particularly interesting and useful is that the initial 1,6 enyne, which undergoes the first ring closing metathesis, is made possible through a vinylic boronic ester.

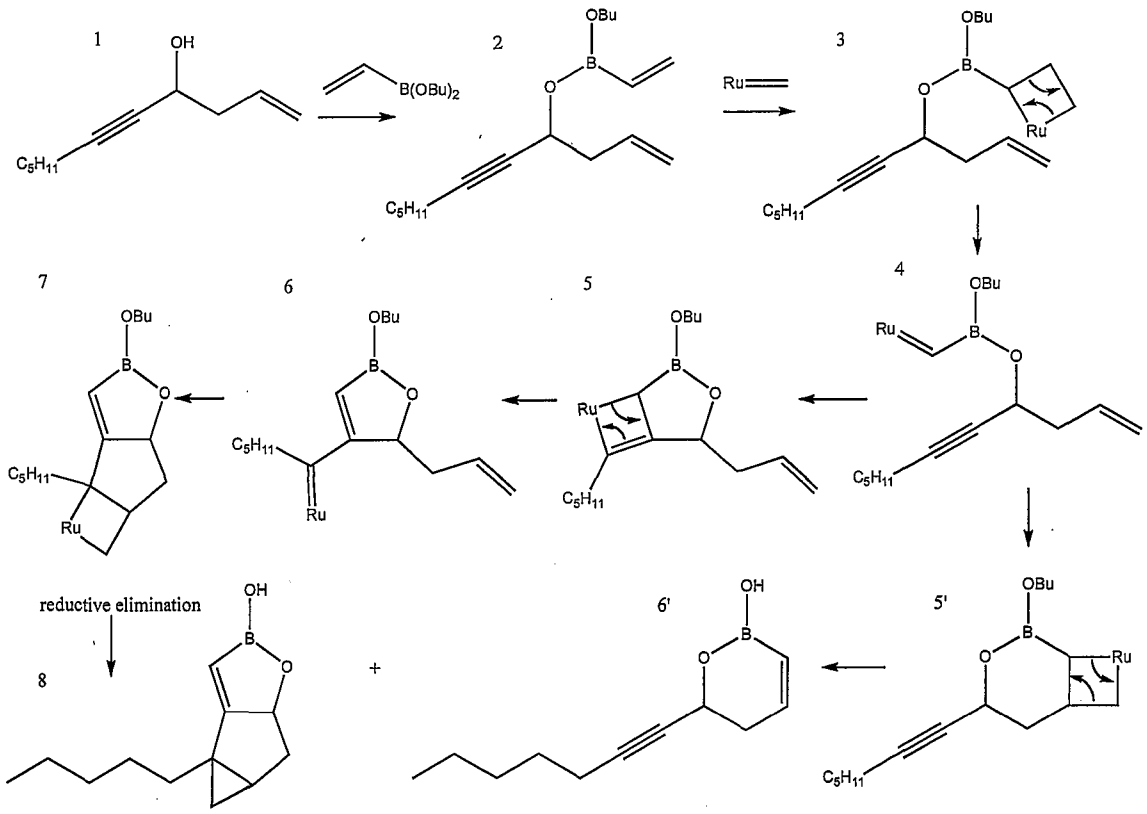
Previous work done by L. McNulty, seen in Scheme 6, has shown that the reaction of 1-undecen-5-yn-4-ol, compound I, with vinyl boronic acid dibutyl ester in the presence of Grubbs first generation catalyst with dichloromethane as solvent produced cyclic boronic acid as well as a polycyclic compound with a cyclopropyl group, compounds II and III, respectively.



Scheme 6. The reaction of 1-undecen-5-yn-4-ol with vinyl boronic acid dibutyl ester in the presence of Grubbs first generation catalyst produces a cyclic boronic acid and a polycyclic boronic acid compound.

The formation of compound II is expected because enyne metathesis has been demonstrated previously with propargyl boronic esters. Compound III would arise from enyne metathesis of alcohol I. However, the formation of the cyclopropane is atypical for

enyne metathesis.[12] The mechanism for the formation of these two products is seen in Scheme 7.

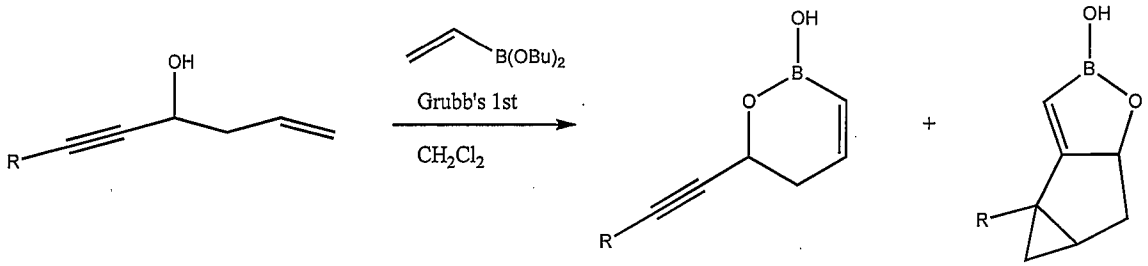


Scheme 7. The mechanism for the metathesis reactions of the vinyl boronic acid of 1-undecen-5-yn-4-ol

The mechanism seen in Scheme 7 is very reminiscent to the mechanism seen in Scheme 4. In step 1, the alcohol starting material reacts with vinyl boronic acid to form the compound in step 2. In the presence of the carbene ruthenium catalyst, a metallocyclobutane is formed when the catalyst reacts with the alkene of the boronic acid. Upon collapsing in step 3, the carbene of step 4 forms. It is from this point that the reaction can proceed in two possible ways. If the carbene reacts with the available alkene, as in step 5', a metallocyclobutane is formed. In step 6', the metallocyclobutane collapses to form 2-hydroxy-5-(1-heptynye) oxaborale and regenerated catalyst. There is

also an alternative mechanism for the formation of this product in which the other alkene forms the carbene before producing the compounds seen in steps 5' and 6'. If the carbene in step 4 reacts with the available alkyne, as in step 5, a metallocyclobutene is formed. In step 6, the metallocyclobutene collapses to form a carbene. Because there is a 1,6 alkene present, the carbene will undergo a tandem metathesis and form a metallocyclobutane in step 7. The ruthenium catalyst is removed via reductive elimination to produce the tricyclic boronic acid of step 8.

In the research presented here, the alkyne substituent of the starting material was varied in order to determine if it has any influence on the distribution of products seen in Scheme 8. A generic rendition of this reaction can be seen in Scheme 8.



Scheme 8. The generic reaction of the reaction seen in Scheme 1, where the substituent on the alkyne can be varied in order to influence product formation.

The substituent was varied by using silyl and methyl groups. In both cases, starting materials had to be synthesized. These two groups were chosen based on the difference in their sizes. In theory, a larger substituent would inhibit the formation of the cyclopropane product because a bulky substituent would obstruct the reaction of the first carbene with the alkyne. Conversely, smaller substituents would not prevent the

formation of any products because the alkyne would not be hindered and free to react with the carbene.

Experimental

General Methods

All reactions were performed under nitrogen. Solvents were taken from a MBraun solvent purification system and were used without further purification. NMR spectra were taken at 20 ° C on a 250 MHz Brucker NMR spectrometer. The 1-undecen-5-yn-1-ol used was previously synthesized in the McNulty lab. The 2-butyn-1-ol and 3-trimethylsilyl-2-propyn-1-ol were purchased from Lancaster. The vinyl boronic acid dibutyl ester, chloroform-d 99.8%D, Grubb's first generation catalyst, allyl magnesium bromide, and PCC were purchased from Aldrich.

Preparation of tricyclic boronic acid, (compound III), and 2-hydroxy-5-(1-heptynye) oxaborole, (compound II), products

Vinyl boronic acid dibutyl ester (1.3 mL, 6.02 mmol), 1-undecen-5-yn-4-ol (0.5 g, 3.01 mmol), and Grubb's first generation catalyst (0.2487 g, 0.301 mmol) in CH_2Cl_2 (15 mL) were refluxed for 24 h. The solution was concentrated under reduced pressure, and then purified by column chromatography with 90% hexanes and 10% ethyl acetate. Solvent was removed.

Compound III, Spectrum 1

^{1}HNMR ($CDCl_3$, 250 MHz) δ0.90 (m, 3H), δ1.35 (m, 2H), δ1.50 (m, 2H), δ2.20 (m, 2H), δ2.50 (m, 2H), δ3.90 (t, 1H), δ5.75 (d, 1H), δ6.85 (m, 1H).

Compound II, Spectrum 2

^{1}HNMR ($CDCl_3$, 250 MHz) δ0.40 (dd, 1H), δ0.90 (m, 3H), δ1.50 (m, 1H), δ2.30 (m, 1H), δ2.80 (m, 1H), δ3.90 (t, 1H), δ5.3 (s, 1H).

Preparation of tricyclic boronic acid, (compound VI), and 2-hydroxy-5-(1-trimethylsilyl) oxaborole, (compound V), products

3-trimethylsilyl-2-propynal To a solution of 3-trimethylsilyl-2-propynol (0.58 mL, 3.89 mmol) in DCM (10mL) was added pyridinium chlorochromate (1.26 g, 5.84 mmol). The reaction was stirred for 1.5 hours then the solvents removed under reduced pressure.

1-trimethylsilyl-5-hexen-1-yn-3-ol (compound IV) To the crude aldehyde previously prepared was added 1.0 M allyl magnesium bromide in THF (4.3 mL, 4.279 mmol) in THF (10 mL) at 0 °C. The reaction was stirred for 1 hour, then quenched with 10% HCl solution and diluted with ether. The organic solution was washed successively with 10% HCl, H_2O, and saturated NaCl solution, dried over $MgSO_4$, and concentrated.

Compound IV, Spectrum 3

^{1}HNMR ($CDCl_3$, 250 MHz) δ0.2 (s, 9H), δ2.25 (t, 2H), δ4.25 (t, 1H), δ5.15 (d, 2H), δ5.9 (m, 1H).

Vinyl boronic acid dibutyl ester (1.3 mL, 6.02 mmol), 1-trimethylsilyl-5-hexen-1-yn-3-ol (0.5 g, 3.01 mmol), and Grubb's first catalyst (0.2487 g, 0.301 mmol) in CH_2Cl_2 (15 mL) were refluxed for 24 h. The solution was concentrated under reduced pressure, and then purified by column chromatography with 95% hexanes and 5% ethyl acetate. Solvent was removed.

Compounds V and VI, Spectrum 4

^{1}HNMR ($CDCl_3$, 250 MHz) δ0.25 (dd, 2H), δ2.30 (t, 1H), δ3.90 (s, 1H), δ4.65 (q), δ5.45 (m), δ6.65 (m).

Compound V, Spectrum 5

^{1}HNMR ($CDCl_3$, 250 MHz) δ 0.20 (s, 9H), δ2.50 (t, 2H), δ4.80 (t, 1H), δ5.70 (d, 1H), δ6.80 (m, 1H).

Preparation of tricyclic boronic acid, (compound IX), and 2-hydroxy-5-(1-methyl) oxaborole, (VIII), products

2-butynal To a solution of 2-butynal (0.53 mL, 7.13 mmol) in DCM (10mL) was added pyridinium chlorochromate (2.305 g, 10.69 mmol). The reaction was stirred for 1.5 hours then the solvent was removed under reduced pressure.

1-hepten-5-yn-4-ol (compound VII) To the crude aldehyde was added 1.0 M allyl magnesium bromide in THF (7.84 mL, 7.84 mmol) in THF (10 mL) at 0 °C. The reaction was stirred for 1 hour, then quenched with 10% HCl solution and diluted with ether. The organic solution was washed successively with 10% HCl, H_2O, and saturated NaCl solution, dried over $MgSO_4$, and concentrated.

Compound VII, Spectrum VI

^{1}HNMR ($CDCl_3$, 250 MHz) δ1.25 (s, 3H), δ2.25 (dd, 2H), δ4.15 (d, 1H), δ5.15 (dd, 2H), δ5.95 (m, 1H).

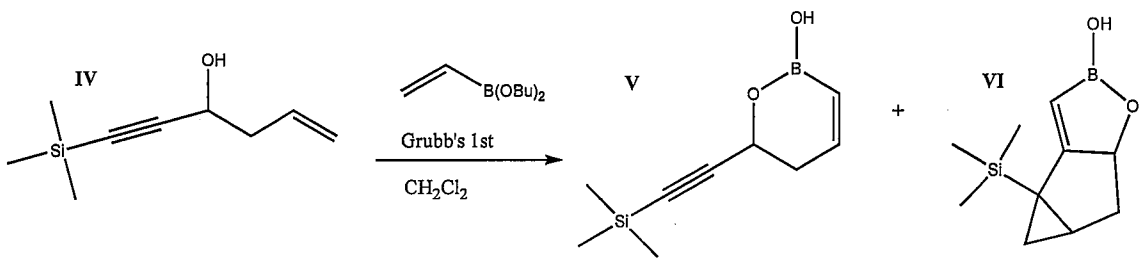
Vinyl boronic acid dibutyl ester (1.3mL, 6.02 mmol), 1-hepten-5-yn-4-ol (0.5 g, 3.01 mmol), and Grubbs first catalyst (0.2487 g, 0.301 mmol) in CH_2Cl_2 (15 mL) were refluxed for 24 h. The solution was concentrated under reduced pressure, and then

purified by column chromatography with 95% hexanes and 5% ethyl acetate. The solvent was removed.

Results and Discussion

For the 1-undecen-5-yn-4-ol metathesis reaction in Scheme 6, certain peaks present in both ^{1}HNMR spectra confirm the presence of both products. One of the most noticeable differences is at δ0.40 in Spectrum 2, which is a doublet of doublets and indicates the presence of the carbon with one hydrogen in the cyclopropane of the tricyclic product. This shift is noticeably not present in Spectrum 1, which is a major factor in showing how only one boronic acid product is present in the first spectrum.

The results of the 1-undecen-5-yn-4-ol metathesis reaction indicate that the pentyl substituent did not favor the formation of one product over the other and appeared to produce them in a one to one ratio. One reason for this outcome could be that the alkyne is not hindered by the pentyl substituent and could undergo metathesis. It was for this reason that further exploration was needed.



Scheme 9. The metathesis of the silyl substituted enyne alcohol with vinyl boronic acid dibutyl ester.

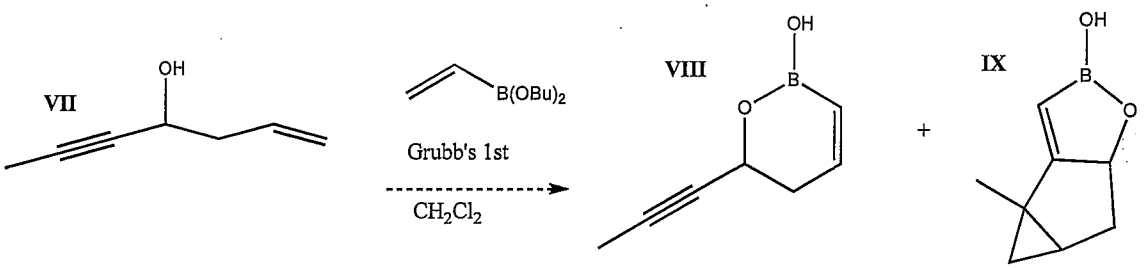
Evidence that the 1-trimethylsilyl-5-hexen-1-yn-3-ol starting material for the metathesis reaction in Scheme 9 was formed is supported by ^{1}HNMR data. Even though both THF and a little starting material are present in the spectrum, the characteristic peaks of the compound can be seen in Spectrum 3. Methyl groups from the silyl group

are at δ0.2, and the secondary carbon with two hydrogens is at δ2.25. The hydrogen of the carbon next to the alcohol is in the electronegative region at δ4.25. The double bond is shown by the peaks at δ5.15 and δ5.9.

A problem, which was consistent with all of the trials of the 1-trimethylsilyl-5-hexen-1-yn-3-ol metathesis reactions, was the presence of the vinyl boronic acid dibutyl ester starting material in the spectra of the products. Many spectra are not fully assigned here because they were not determined to be clean or conclusive enough. Spectrum 4 gives evidence that only one product was formed, but the presence of starting material complicates the spectrum. The trimethylsilyl substituted tricyclic boronic acid is present as evidenced by the characteristic δ.25 shift, similar to that seen in Spectrum 2 with the pentyl substituted tricyclic boronic acid for the hydrogen bound to the carbon of the cyclopropane ring. Spectrum 5, which is of later column fractions of this reaction, does not have the characteristic cyclopropane signal at δ.25 seen in Spectrum 4. The doublet of doublets at δ4.80 and δ4.75 in the two spectra shows the presence of the hydrogen on the carbon, which is next door to the alkyne on 2-hydroxy-5-(1-trimethylsilyl) oxaborole.

The results of the 1-trimethylsilyl-5-hexen-1-yn-3-ol metathesis reaction support the theory that a bulky substitutent on the alkyne can limit the formation of the tricyclic boronic acid product. According to the integration, 2-hydroxy-5-(1-trimethylsilyl) oxaborole was favored over the trimethylsilyl substituted tricyclic boronic acid product by a 2:1 ratio. This spectrum was from the first set of column fractions out of three that were run. There was no tricyclic boronic acid product in the later fractions, according to ^{1}HNMR. This indicates that the overall product ratio favors the 2-hydroxy-5-(1-trimethylsilyl) oxaborole much more than the tricyclic product.

Evidence that the 1-hepten-5-yn-4-ol starting material was formed is supported by ^{1}HNMR data in Spectrum 3. The data seen is very similar to that of 1-trimethylsilyl-5-hexen-1-yn-3-ol. The methyl group of the heptenynal starting material is shifted higher due to being closer to the triple bond and is seen at δ1.25. Just as in the silyl starting material, the hydrogens on the secondary carbon are at δ2.25. The hydrogen on the same carbon as the alcohol has shifted only slightly and is at δ4.15. Again, similar to the other starting material, the hydrogens on the carbons of the double bonds peaks are shown at δ5.15 and δ5.95.



Scheme 10. The metathesis of the methyl substituted enyne alcohol with vinyl boronic acid dibutyl ester.

The spectra of the 1-hepten-5-yn-4-ol metathesis reaction products will not be discussed because the results were not very conclusive. Initial spectra still contained substantial starting material and vinyl boronic acid. Others contained too many solvents. The solvents from the reaction and column proved difficult to remove even after the solution was placed under reduced pressure.

Conclusion

The variation of the alkyne substituent of the enyne alcohol starting material of the metathesis reactions gave mixed results. The trimethylsilyl substituent showed that use of a bulkier substituent favors the formation of the oxaborole. Results for the methyl

substituent were inconclusive, so further research should be done with this starting material in order to determine if the tricyclic boronic acid forms or not. If this reaction were to proceed, then the spectrum would be easier to interpret due to the simpler nature of the alkyl chain. In order to test the theory of the substituent influencing the formation of certain metathesis products, the metathesis preferences of several other alkyl substituted starting materials should be investigated. Perhaps then can a better trend in product preference be determined.

Acknowledgements

Meagan would like to thank her thesis advisor, LuAnne McNulty, for her support in the laboratory and her encouragement to work independently. Thanks is given, also, to Butler University and the honors program for the chance to write an undergraduate thesis.

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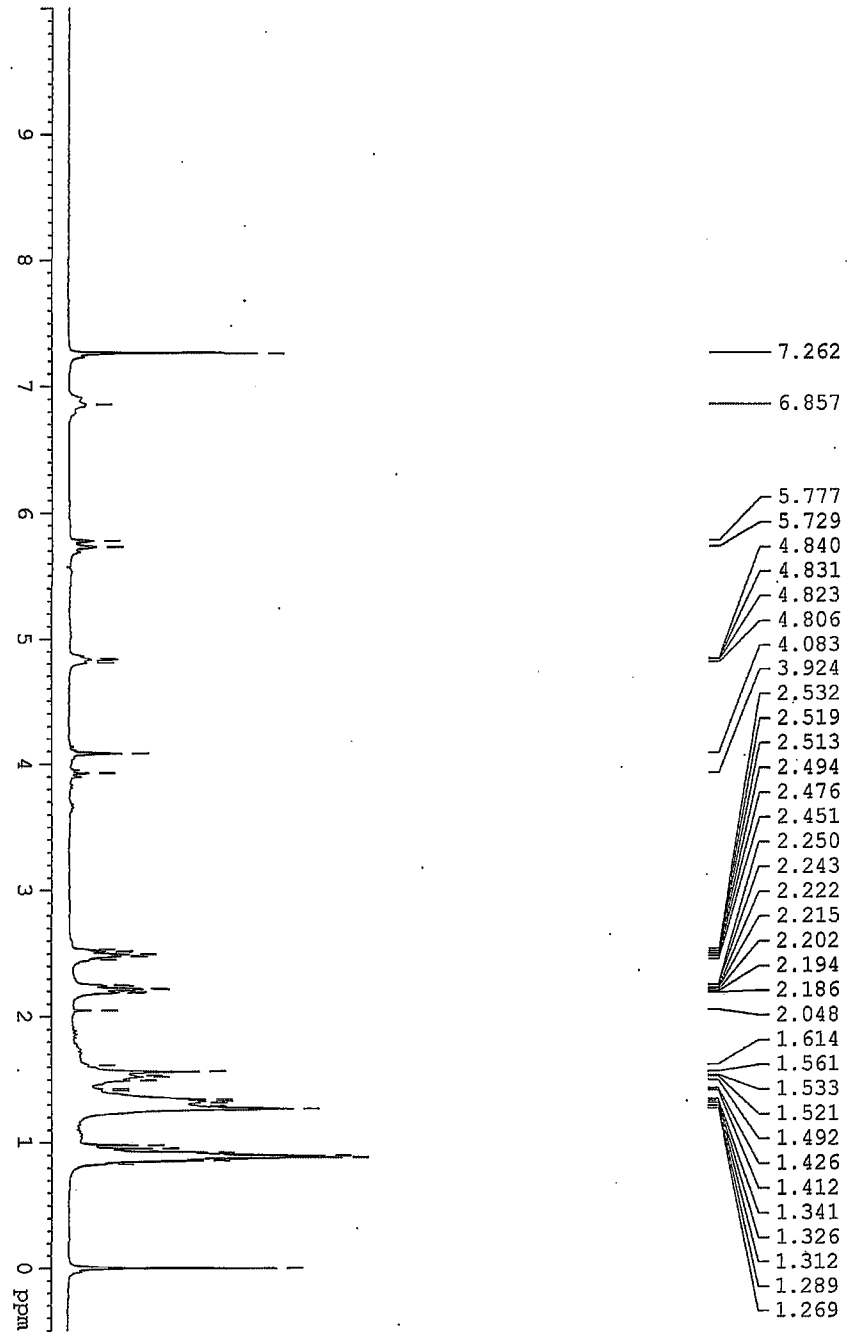
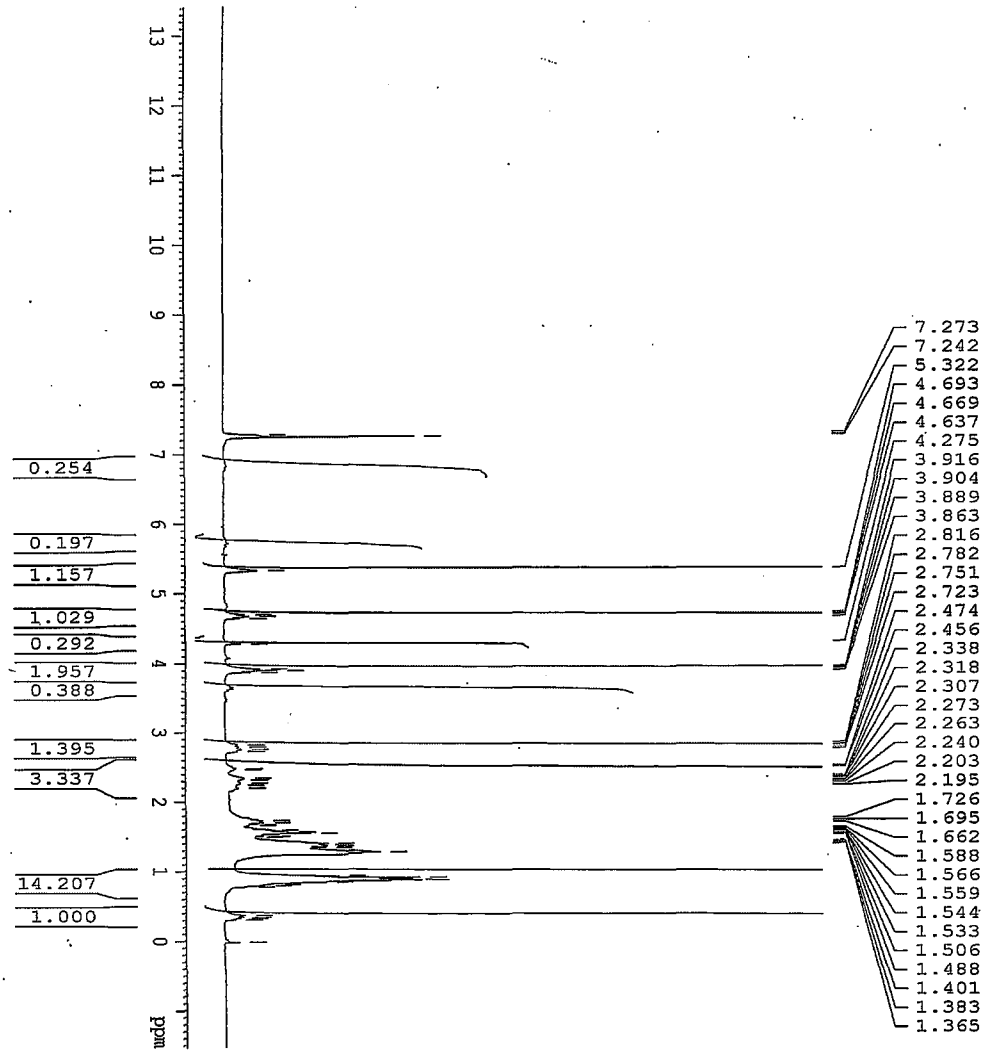
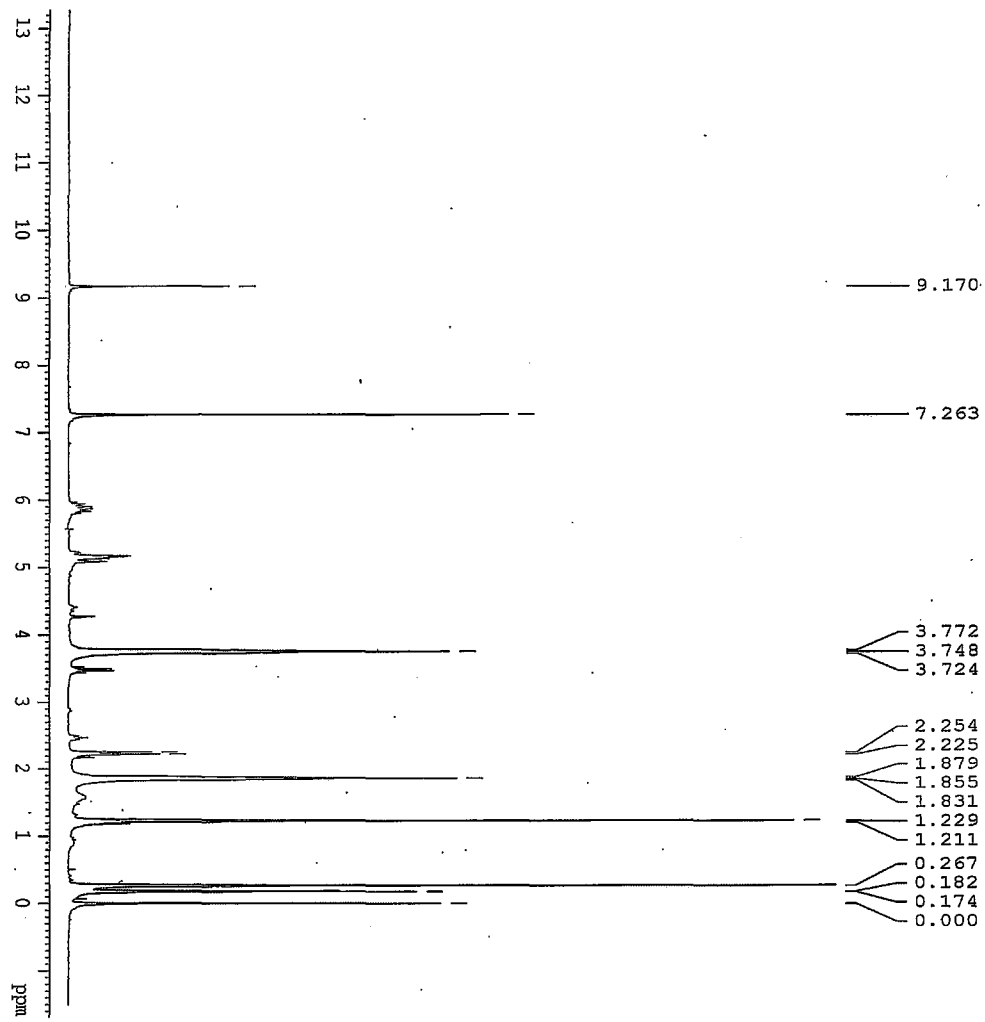
Reference Spectra



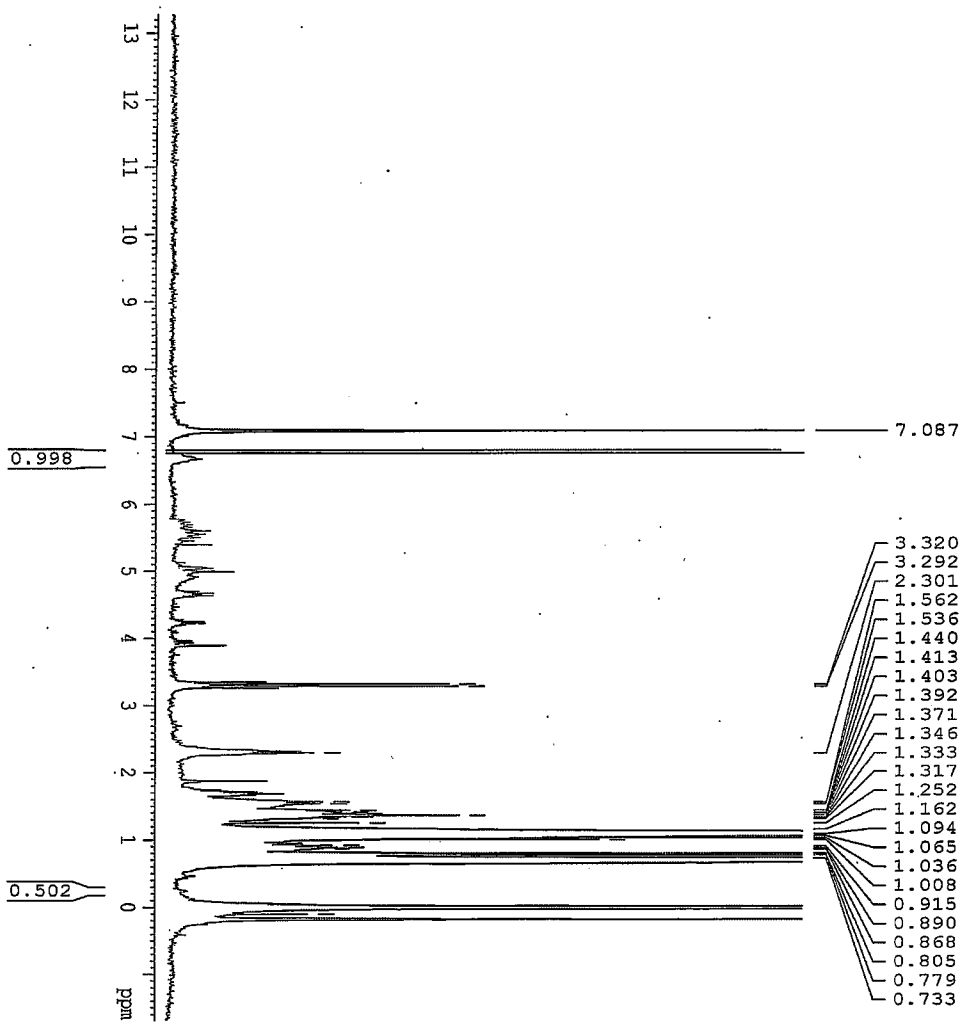
Spectrum 1. 2-hydroxy-5-(1-heptynye) oxaborole



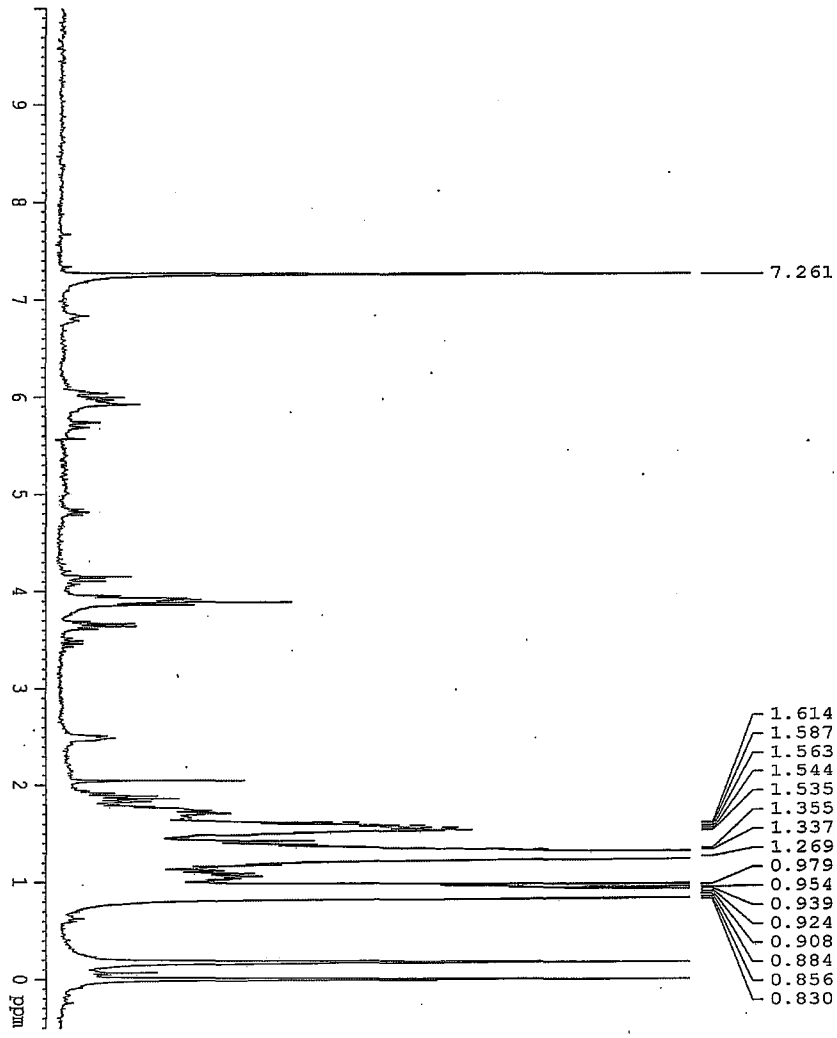
Spectrum 2. heptyne substituted tricyclic boronic acid



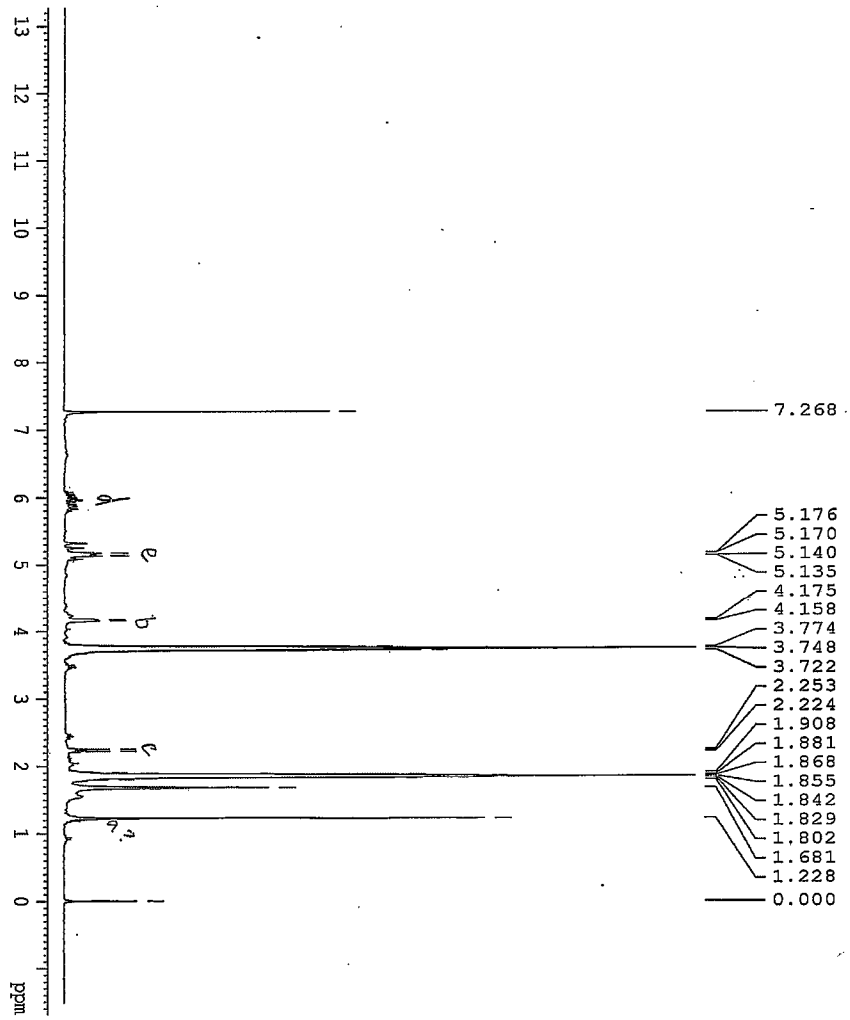
Spectrum 3. 1-trimethylsilyl-5-hexen-1-yn-3-ol



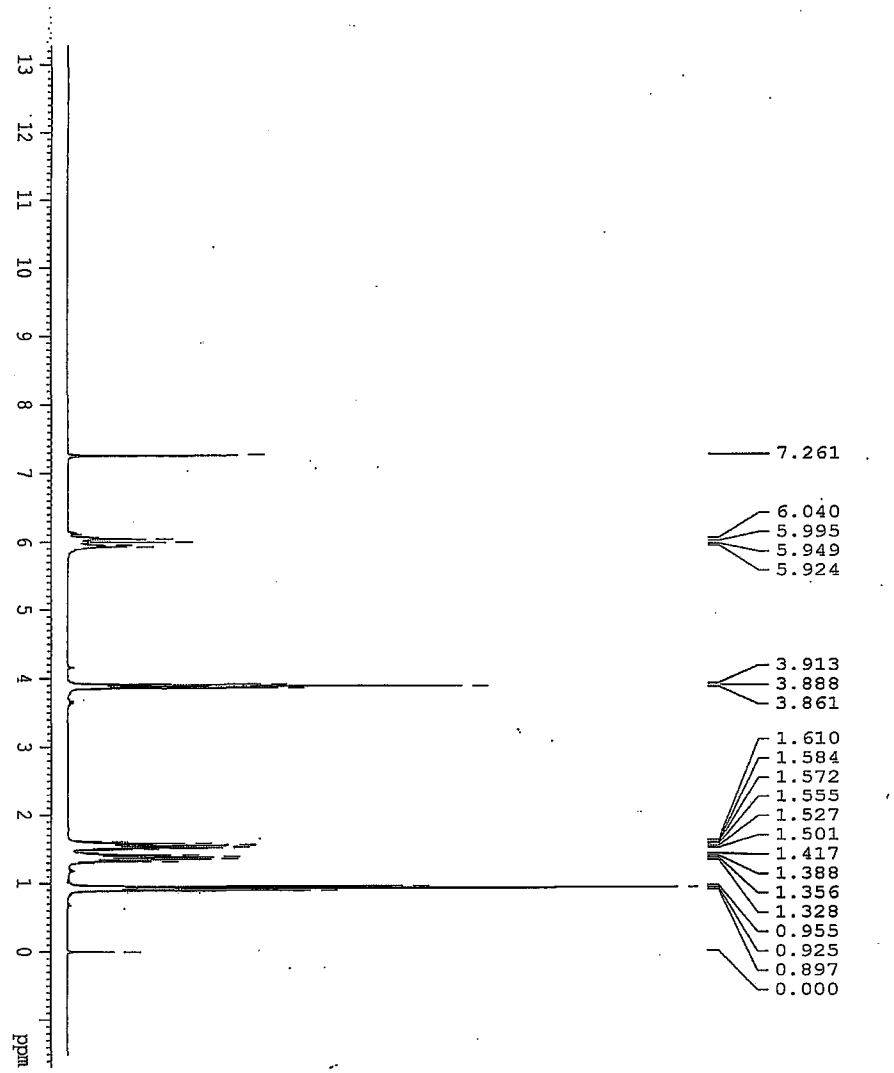
Spectrum 4. Mixture of trimethylsilyl substituted tricyclic boronic acid and 2-hydroxy-5-(1-trimethylsilyl) oxaborole



Spectrum 5. 2-hydroxy-5-(1-trimethylsilyl) oxaborole



Spectrum 6. 1-hepten-5-yn-4-ol



Spectrum 7. Vinyl boronic acid dibutyl ester