STUDIES TOWARDS SYNTHESIS OF PARACONIC ACIDS

by

Karenia Soto

A Thesis Submitted to the Faculty of

The Wilkes Honors College

in Partial Fulfillment of the Requirements for the Degree of

Bachelor of Arts in Liberal Arts and Sciences

with a Concentration in Biological Chemistry

Wilkes Honors College of

Florida Atlantic University

Jupiter, FL

May, 2011

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This thesis was prepared under the direction of the candidate's thesis advisor, Dr. Veljko Dragojlovic, and has been approved by the members of his supervisory committee. It was submitted to the faculty of The Honors College and was accepted in partial fulfillment of the requirements for the degree of Bachelor of Arts in Liberal Arts and Sciences.

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ACKNOWLEDGEMENTS

I would like to thank Dr. Veljko Dragojlovic and Dr. Michelle Ivey for all their help and patience. I would like to thank my family and Alejandro Landa for their support and love. Also, I would like to thank Kevin Pels for all of the helpful discussions and editing. Lastly, I would like to thank Wilkes Honors College of Florida Atlantic University and its faculty members for their encouragement and willingness to always help.

ABSTRACT

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Title:	Studies Towards Synthesis of Paraconic Acids
Institution:	Wilkes Honors College of Florida Atlantic University
Thesis Advisor:	Dr. Veljko Dragojlovic
Degree:	Bachelor of Arts in Liberal Arts and Sciences
Concentration:	Biological Chemistry
Year:	2011

Paraconic acids are naturally occurring compounds synthesized by bacteria and fungi. They are known for having antitumor and antibiotic properties. By use of a phase-vanishing (PV) halolactonization with PTFE (Teflon) as a phase screen, we were able to synthesize precursors to these compounds. The PV-PTFE halolactonization of alkenoic acids with iodine monochloride gave the corresponding iodolactones, while halolactonization with bromine gave the corresponding bromolactone. Halolactonization of 4-pentenoic acid with water as a solvent also gave good results. Future experiments will explore the synthesis of further precursors by means of a photolytic carbonylation of iodolactone and a phenylation-ruthenium tetroxide oxidation sequence.

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INTRODUCTION

Paraconic Acids

Lichen symbiont is a composite organism formed from the symbiosis of fungi and algae. Studies have found that these organisms are capable of producing secondary metabolites that have antibiotic, antitumor and antineoplastic properties.[1] Among many of the compounds that *Lichen* symbionts produce, paraconic acids are among the most common. Paraconic acids are naturally occurring compounds that contain a γ-butyrolactones skeleton (Figure 1, structure **13**) with a carboxylic group in carbon 3 and substituents in carbon 2 and 4 positions (Figure 1, structure **1-12**).[2] γ-Butyrolactone skeleton is present in about 10% of all natural products. [4,5] Figure 1 shows paraconic acids as well as a number of structurally related natural products .

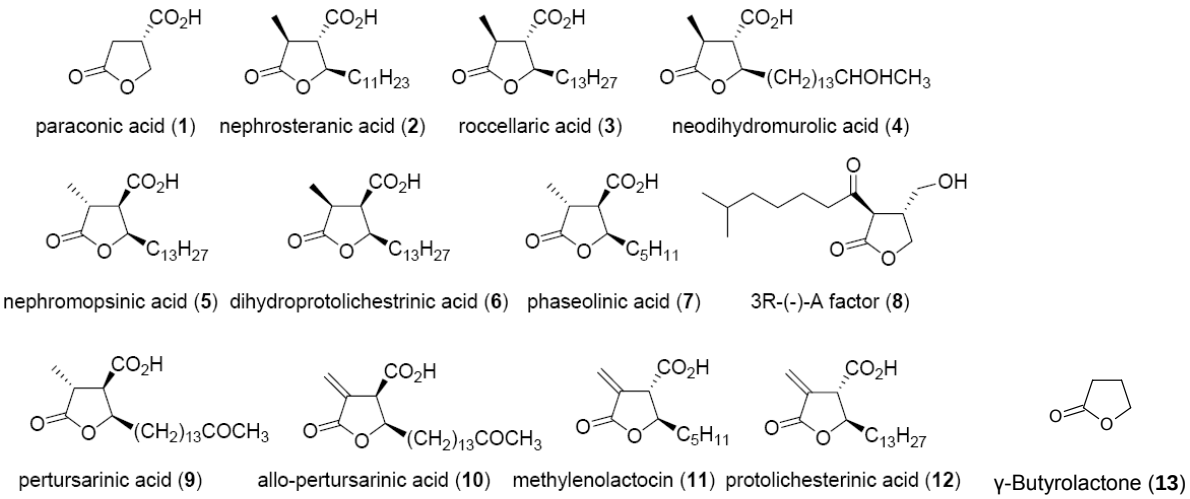
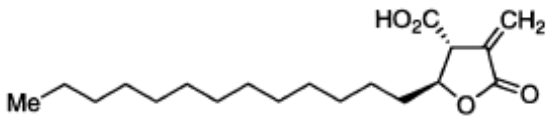


Figure 1. *Natural occurring paraconic acids*

(+)-Protolichesterinic acid (Figure 2) is one of the secondary metabolites belonging to the paraconic acid family.[3] This compound has been shown to have important biological activities. First, the lichen metabolite serves as an inhibitor of DNA polymerase, an enzyme responsible for the replication of DNA. Second, it inhibits DNA

ligase, an enzyme essential in DNA replication and repair.[6] Both of these actions disable bacteria from replicating their genetic material, thus (+)-protolichesterinic acid is a potential antibiotic for humans. Other secondary metabolites are potential herbicides. Furthermore, they exhibit toxic and antifeedant properties towards other organisms.[3]



14

Figure 2. *(+)-Protolichesterinic acid* ***14***

Due to their potential pharmaceutical uses, synthesis of paraconic acids has gain much attention from the chemistry community.[7,8] Furthermore, paraconic acids from natural sources have been found to be difficult to separate.[9] For this reason, many synthetic approaches have been developed for the synthesis of paraconic acids and their derivatives.[7,9] Comini et al. reported that chiral derivatives of the acid, such as 2-alkylparaconic acid, served as useful building blocks for paraconic acid synthesis. Unfortunately, such derivatives are difficult to prepare with the use of current methods.[11,12] However, Turova et al. proposed the synthesis of 2-alkylparaconic acid through the asymmetric hydrogenation of acylsuccinates in the presence of catalytic system $RuCl_3$–atropisomeric diphosphine, with enantioselectivities of up to 99.5%.[9] Selvakumar et al. reported a high yield of paraconic acid derivatives through the cyclization of highly electron-deficient dienes.[7] Dias et al. demonstrated that dihydroxylation of unsaturated *syn*-aldol adducts produces adequate levels of diastereoselectivity to give trisubstituted γ-butyrolactone derivatives.[13] Drake et al. reported successful halolactonization of 4-pentenoic acid in the presence of hydrogen peroxide and sodium bromide with arylseleninic acid as the catalyst.[14] Although of all of

these methods are reliable for the synthesis of paraconic acids and their derivatives, they make use of expensive and hazardous reagents. However, in 2008, Dragojlovic and Windmon developed an environmentally friendly and more efficient alternative halolactonization method. In their study, phase-vanishing reactions were used on neat reagents. This method simplified the reaction workup and improved yields.[14] A recent application to phase vanishing reactions was introduced by Soto and Dragojlovic. They developed a laboratory design which allowed for both a free radical bromination of an alkene and addition of hydrogen bromide to an alkene to be simultaneously carried out.[24] More recently, Dragojlovic and Van Zee improved the use of phase-vanishing reactions when they proposed the use of Teflon (PTFE) as a phase screen in halolactonization reactions, instead of FC-72 (C_6F_{14}).[16] Pels and Dragojlovic further studied the use of Teflon as a phase screen. In their study, they applied a solvent-free PV-PTFE reactions setup. This experimental setup proved to be easier and inexpensive, while providing products in high yield and purity.[23]

Phase-Vanishing Reactions

Phase-vanishing (PV) reactions were introduced by Curran,[19] Rye,[21] and Verkade.[20] PV reactions are triphasic and include a reagent, a liquid perfluoroalkane as a phase screen, and a substrate.[15,18] The perfluoroalkane does not react with either of the reagents and it allows for their separation.[15]

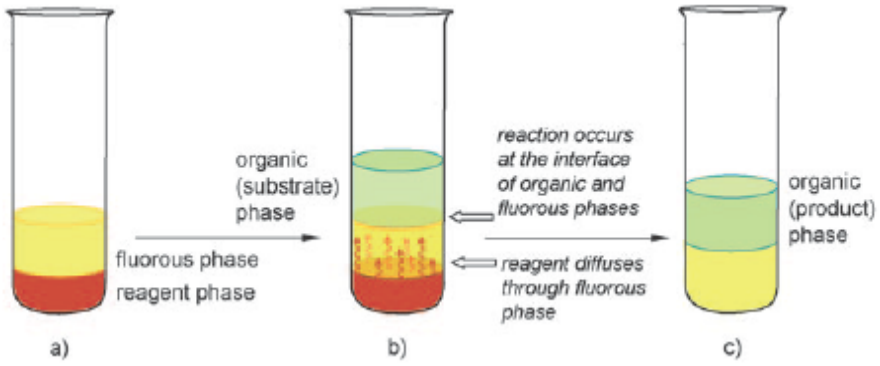


Figure 3. *Phase-vanishing reaction (Figure taken from European Journal of Organic Chemistry).*

Figure 3 shows the setup for a phase-vanishing reaction. The most dense reagent layer is at the bottom (Figure 3a), while the least dense organic layer lies on top (Figure 3b). A phase screen of an intermediate density is between the two. The reaction takes place when the more dense reagent layer diffuses through the FC-72 layer and slowly reacts with the organic layer (Figure 3c).[18] PV reactions allow for a slow and controlled delivery of reagents which prevents vigorous reactions that could take place if the reagents were mixed rapidly.[15,18,19] Furthermore, these reactions involve simple workup and provide high yields. Although FC-72 can be recycled after each reaction and reused, its use has some disadvantages. First, FC-72 is an expensive substance.[22] Second, it has a high global warming potential (GWP ~10,000) and atmospheric lifetime of 3200 years.[16,17] Lastly, due to their dependence on density, PV reactions have limited applications.[22] The use of Teflon as a phase screen, as proposed by Van Zee and Dragojlovic, eliminates the disadvantages posed by FC-72. Thus, in this study we will use Teflon as a phase screen in the halolactonization of alkenoic acids and their ester. Furthermore, we will investigate the use of water as a solvent in a halolactonization reaction as opposed to a phase vanishing reaction setup.

Application of Phase Vanishing Reactions

In our study of phase vanishing reactions, we developed a reaction setup that allowed for organic chemistry students to perform a simultaneous free radical bromination of an alkylbenzene and an addition of hydrogen bromide to an alkene (Figure 4). In an undergraduate laboratory exercise involving a free radical bromination, hydrogen bromide (HBr) is usually an undesired side product, whose handling presents a problem. Our reaction setup allows for HBr to be used in an electrophilic addition to an alkene instead of being wasted.

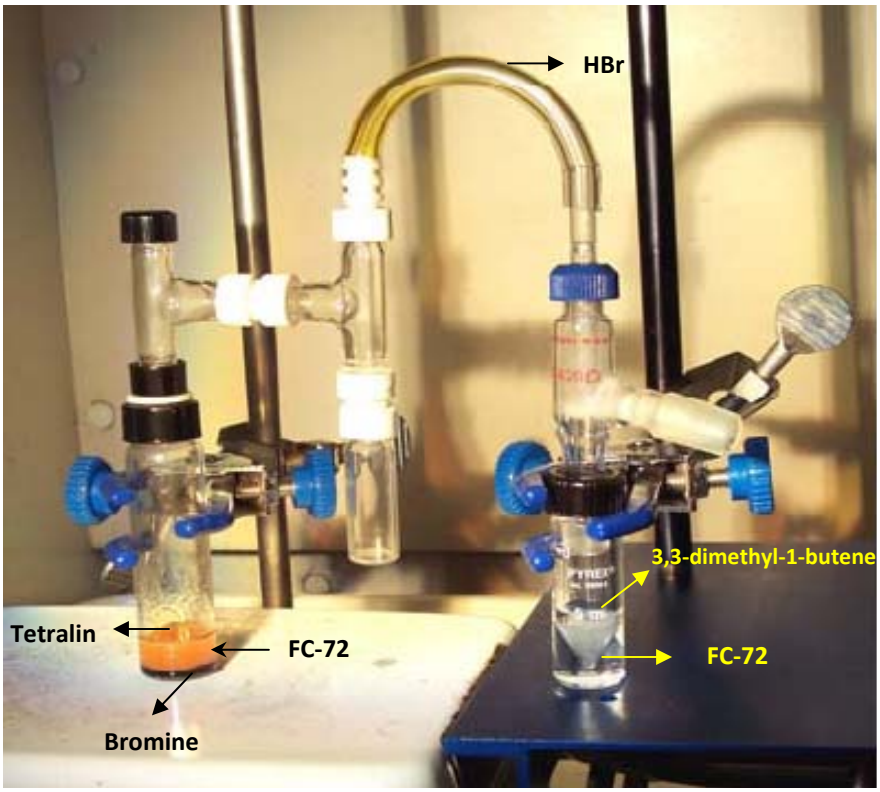


Figure 4. *Reaction setup developed for simultaneous free radical bromination and electrophilic addition of an alkene.*

Furthermore, our laboratory design not only provided students an exercise involving phase vanishing reactions, but also encouraged them to consider regioselectivity of free radical reactions.

MATERIALS AND METHODS

General

Data Acquisition

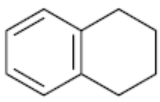
GC-MS analyses were performed by means of Agilent 6890N Gas Chromatograph equipped with an HP-5MS 30 m x 0.25 mm column (Cat. No. 19091S-433) and Agilent 5973N MSD. The crude products were isolated and analyzed by GC-MS. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$

Solvents and Reagents

Bromine, 4-pentenoic acid, 3-butenoic acid, menthol, iodine, tetralin, 3,3-dimethyl-1-butene, perflourohexane (FC-72), sodium thiosulfate and magnesium chloride were obtained from Sigma-Aldrich. All solvents (dichloromethane and diethyl ether) were purchased through either Sigma Aldrich or Fisher Scientific. Reagents and solvents were used as purchased.

Experimental Procedures

*Free radical bromination of tetralin **15** and addition of hydrogen bromide to 3,3-dimethyl-1-butene **16***



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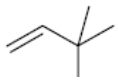

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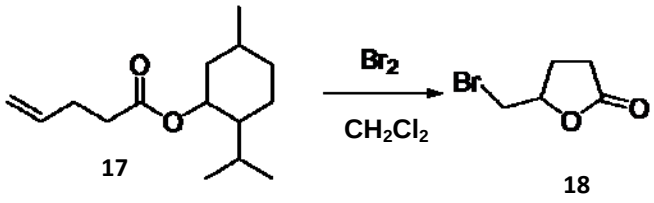
An apparatus as shown in Figure 4 was assembled. Bromine (0.64 g) was overlaid with FC-72 (1.0 mL), followed by addition of tetralin **15** (0.13 mL, 0.13 g) to the top of FC-72. A stirring bar, 1.0 mL of FC-72 and 0.13 mL (0.084 g) of 3,3-dimethyl-1-butene **16** dissolved in either 1.0 mL of either dichlormethane or acetic acid were added to a 3 mL receiving vial. For a better control of the reaction rate and to avoid early evolution of HBr, the complete apparatus was assembled while fumehood lights were turned off. The fumehood lights, an overhead projector, or a 40W light bulb, were turned on and the reaction was continued for as long as there was evolution of HBr (~20 min.). The desired product in the reaction vial was colorless and it was dissolved in dichloromethane. Dichloromethane extract was rinsed with 1.0 mL of water, followed by a rinse with 1.0 mL of aqueous sodium chloride and dried with anhydrous magnesium sulfate. The dichloromethane solution was analyzed by GC-MS.

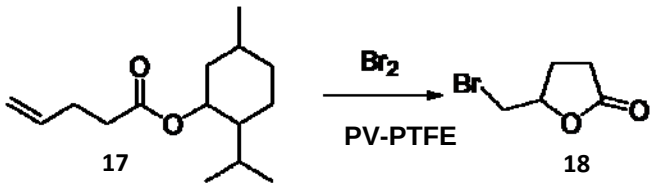
The contents of the receiving flask were transferred into a separatory funnel and, if acetic acid was the solvent, dichloromethane (2 mL) and water (1 mL) were added. If dichloromethane was a solvent, an additional 1.0 mL of it and water (1 mL) were added. Dichloromethane solution was drained into a 10 mL Erlenmeyer flask and 1.0 mL of saturated solution of sodium bicarbonate was added. The solution was stirred until the effervescence stopped. The solution was returned to a separatory funnel and the layers were separated. The dichloromethane solution was rinsed with an additional 1.0 mL of saturated solution of sodium bicarbonate, followed by a rinse with 1.0 mL of aqueous sodium chloride. The solution was dried with anhydrous magnesium sulfate and analyzed by GC-MS (Appendix, Figure 14-22).

Immersed Bromination and Bromolactonization of Menthyl 4-pentanoate **17**



A stirring bar, menthyl 4-pentanoate **17** (0.3 mL) and dichloromethane (3 mL) were placed in a 25 mL round bottom flask. Bromine (0.1 mL) was added to a PTFE sealed delivery tube. The delivery tube was immersed into the solvent and reaction was kept under slow stirring, which was continued for 25 minutes. The dichloromethane solution was treated with sodium thiosulfate to remove any excess bromine. The bottom layer was collected and analyzed. The product was evaporated and purified by means of rotary chromatography (Harrison Chromatotron, eluting with 3:1 hexanes/ether).

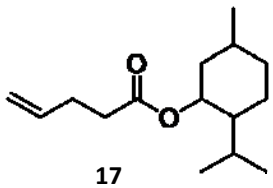
*Solvent-Free Immersed Bromination and Bromolactonization of Menthyl Ester **15***



A stirring bar and menthyl 4-pentanoate (0.3 mL) were placed in a 25 mL round bottom flask. Bromine (0.1 mL) was added to a PTFE sealed delivery tube. The delivery tube was immersed into the substrate and reaction was kept under slow stirring. The stirring was continued for 25 minutes. Product was dissolved in dichloromethane and treated with sodium thiosulfate. The bottom layer was collected and analyzed. The

product was evaporated and purified by means of rotary chromatography (Harrison Chromatotron, eluting with 3:1 hexanes/ether).

*Vapor-Phase Bromination and Bromolactonization of Menthyl 4-pentanoate **17***



17

A stirring bar and menthyl 4-pentanoate **17** (0.3 mL) were placed in a 25 mL round flask. Bromine (0.1 mL) was added to a PTFE sealed delivery tube. The delivery tube was inserted into the flask, but not immersed into the substrate and reaction was kept under slow stirring (Figure 5). The stirring was continued for 25 minutes. Product was dissolved in dichloromethane and treated with sodium thiosulfate. The bottom layer was collected and analyzed. The product was evaporated and purified by means of rotary chromatography (Harrison Chromatotron, eluting with 3:1 hexanes/ether).

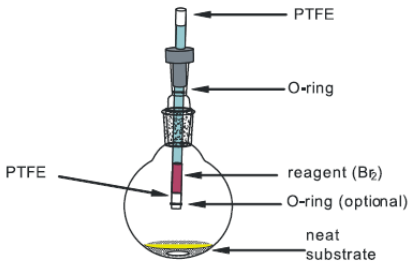
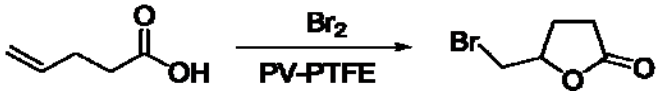


***Figure 5.** Reaction setup for vapor-phase bromination and bromolactonization of menthyl 4-pentanoate **17**.*

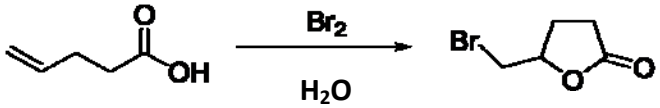
*Bromination and Bromolactonization of 4-pentenoic acid **19***



19 **18**

A stirring bar, 4-pentenoic acid **19** (0.33 mL) and dry dichlomethane (4 mL) were added to a 25 mL round flask. Bromine (0.08 mL) was added to a sealed PTFE delivery tube. The delivery tube was immersed into solvent to begin reaction. Reaction was kept under slow stirring. The average reaction time was 20 minutes. The dichloromethane solution was treated with sodium thiosulfate. The bottom layer was collected, analyzed and evaporated. The evaporated material was then purified by means of rotary chromatography (Harrison Chromatotron, eluting with 3:1 hexanes/ether).

*Bromination and Bromolactonization of 4-pentenoic acid (**19**) in the presence of water*



19 **18**

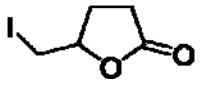
A stirring bar, 4-pentenoic acid **19** (1 mL), water (100 mL) were added to a 200 mL round flask followed by bromine (0.5 mL). The reaction was kept under fast stirring. The average reaction time was around one hour. Sodium chloride was added to reaction after an hour. Solution was extracted with dichloromethane and the extract was rinsed with sodium thiosulfate, water and then sodium chloride. Top layer was dried with magnesium chloride and then filtered and evaporated.

*Ionization and Iodilactonization of 4-pentenoic acid **19***

19 **20**

A stirring bar and 4-pentenoic acid **19** (0.3 mL) were added to a 25 mL round bottom flask. Iodine monochloride (0.1 mL) was added to a sealed PTFE delivery tube. The delivery tube was immersed into the substrate and reaction was kept under slow stirring. The average reaction time was 15 minutes. Product was treated with sodium thiosulfate and bottom layer was collected and analyzed in GC-MS.

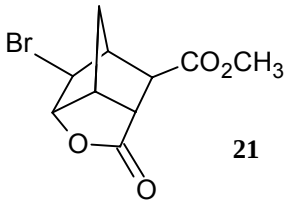
*Cobalt-Catalyzed Carbonylation of Iodolactone **20***



20

Cobalt (II) acetylacetonate (0.08 g) was dissolved in 7.5 mL of methanol:acetone (3:1) solvent. Iodolactone **20** (0.02 g) was dissolved in 7.5 mL of methanol:acetone (3:1). Both solutions were mixed and placed in an Ace photochemical reaction assembly (Cat. No. Z214558-1EA). The first 10 minutes, carbon monoxide was bubbled through the reaction solution. After 10 minutes, a carbon monoxide delivery tube was placed above the surface of the solution, the UV lamp (5.5 W) was turned on and irradiation was continued for 24 hours. Product was filtered through Florisil (60-100 mesh) and analyzed by means of GC-MS.

*Cobalt-Catalyzed Carbonylation of Bromolactone **21***



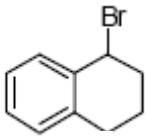
21

Cobalt (II) acetylacetonate (0.08 g) was dissolved in 7.5 mL of methanol:acetone (3:1) solvent. Bromolactone **21** (0.24 g) was dissolved in 7.5 mL of methanol:acetone (3:1). Both solutions were mixed and placed in an Ace photochemical reaction assembly (Cat. No. Z214558-1EA). The first 10 minutes, carbon monoxide was bubbled through the reaction solution. After 10 minutes, a carbon monoxide delivery tube was placed above the surface of the solution, the UV lamp (5.5 W) was turned on and irradiation was continued for 24 hours. Product was filtered through Florisil (60-100 mesh) and analyzed by means of GC-MS

RESULTS AND DISCUSSION

Free Radical Bromination of an Alkylbenzene and Addition of HBr to an Alkene

In the laboratory experiment that we designed, students were asked to predict the outcome of the free radical bromination of tetralin **15**. For the free radical bromination of tetralin, students almost exclusively proposed a monobromination product **22** (Figure 6); however, they were told about the possibility of polysubstitution.



22

Figure 6. *Product predicted by students in the free radical bromination of tetralin*

When samples were analyzed in the GC-MS, the major products were naphthalene (**24**), 1-bromonaphthalene (**25**) and 1,4-dibromonaphthalene (**26**) (Appendix, Figure **14**) instead of the expected 1,1,4,4-tetrabromotetralin (**23**) (Figure 7).

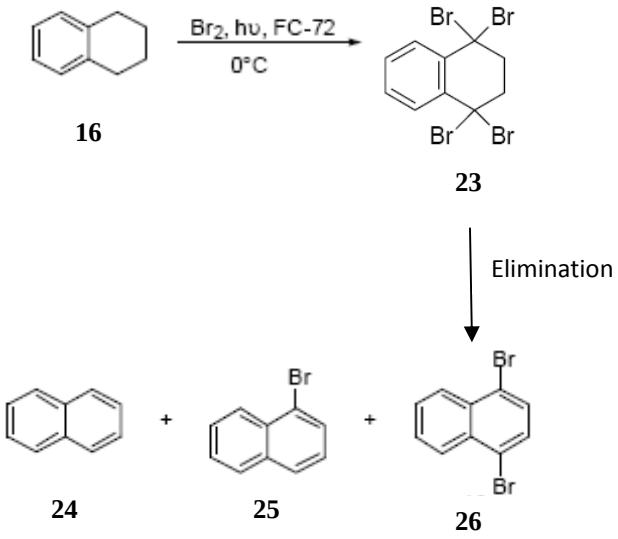


Figure 7. *Major products of free radical bromination of tetralin (**15**).*

These results allowed for us to discuss with the students that the reason for such an easy elimination of compound **23** was the formation of an additional aromatic ring.

Bromination of 3,3-dimethyl-1-butene **21** also gave unexpected results for the students as well as for us. Commercially available alkene contains 50-150 ppm of 2,6-di*t*-butyl-4-methylphenol (BHT) as a stabilizer, which we expected to suppress free radical reactions. Even though we used 3,3-dimethyl-1-butene without any purification, in dichloromethane as a solvent, an apparent free radical addition gave 1-bromo-3,3-dimethylbutane (**27**) as the major product (Appendix, Figure 15,18 and 19).

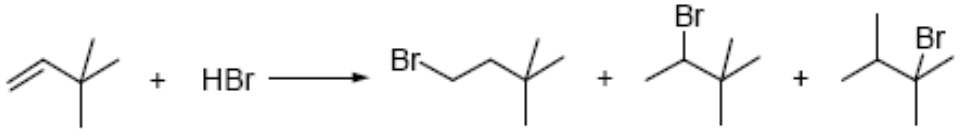


Figure 8. *Products of the addition of hydrogen bromide to alkene* ***20****.*

According to Markovnikov's rule, compound **29** should have been the major product because it produces the most stable carbocation (Figure 8). Prolonged reaction times (~30 minutes or longer) seem to favor free radical addition. It has been reported that addition of zinc dust to an alkene prevents free radical addition from occurring.[26] However, when we carried out the reaction by bubbling HBr through a solution of alkene in acetic acid, addition of zinc dust did not appear to have any effect (Appendix, Figure 16 and 17). In order to achieve an electrophilic addition, reactions should be carried out for shorter times and HBr should be produced in a large excess (faster bubbling) since slow bubbling appeared to favor free radical addition.

Synthesis of Paraconic Acids

We carried out synthesis of halolactones **18** and **20** by the cyclization of either the ester **15** or the acid **17**. While small esters, such as methyl 4-pentenoate, worked very well, we were not able to cyclize the corresponding menthyl esters **17** (Figure 9). We hypothesized that steric hindrance prevented the reaction from proceeding in the expected 5-carbon ring configuration. The mechanism for the bromination and bromolactonization of compound **17** is shown in Figure 9. Although it has been reported that the mechanism

involves attack of the carbonyl carbon, it is possible that it is the alkoxy carbon that is involved.

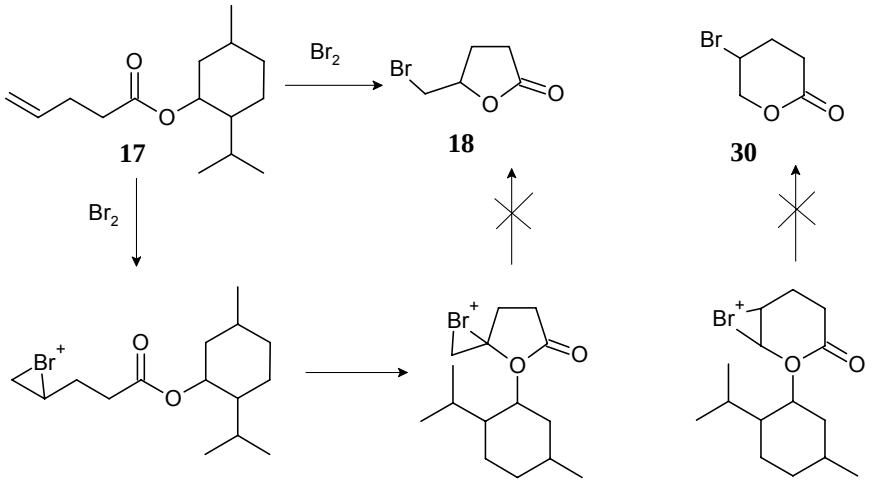
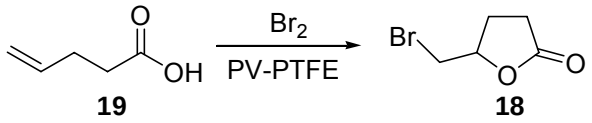


Figure 9. *Mechanism for attempted asymmetric halolactonization of menthyl 4-pentenoate* ***17***

Table 1 shows the yields obtained from the bromination and bromolactonization of 4-pentenoic acid. The best yields and highest purity was obtained in the bromolactonization of compound **18** in the presence of water (Table 1, Entry 3).

Table 1. Bromination and bromolactonization of 4-pentenoic acid **19**



19 **18**

Entry	Conditions	**18**(%)[a]
1	Br/PTFE/rt, 20 min	50-70[b]
2	Br/PTFE/CH_2Cl_2/rt, 25 min	25.3
3	Br/H_2O/rt, 60 min	87.7

[a]GC yields. [b]Isolated yields.

The use of water allows for the hydrophobic organic reagents to come in closer contact during the reaction. Alternatively, the bromolactonization of 4-pentenoic acid gave high yields of bromolactone **18**; however, reproducibility of the reaction was poor (Entry 1, Table 1). Unlike Van Zee and Dragojlovic[18,22], who obtained high yields, bromolactonization of 4-pentenoic acid in the presence of dichloromethane (Entry 2, Table 1) gave poor yields. Furthermore, the bromolactone **18** was obtained with some impurities. Bromolactone **18** was relative unstable, thus purification using rotary and column chromatography many times resulted in the loss of the compound. This could be due to the high volatile properties of compound **18**.

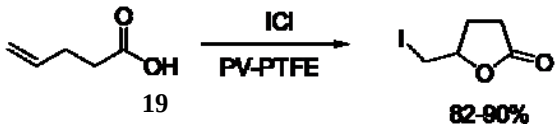


Figure 10. *Iodolactonization of 4-pentenoic acid* ***19***

The PV-PTFE iodolactonization of 4-pentenoic acid **19** with iodine monochloride resulted in better yields than bromine (Figure 10). Furthermore, the reaction rate for halocyclization of 4-pentenoic acid **19** was increased using iodine monochloride.

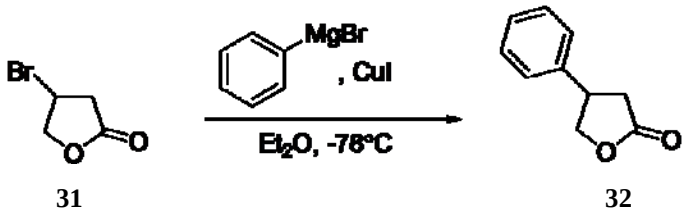


Figure 11. *Grignard reaction of bromolactone* ***31***

An organocopper coupling reaction (Figure 11) was performed on bromolactone **31**; however, it was not successful. We hypothesized that use of copper (I) bromide as oppose to the more reactive copper (II) iodide may have contributed to this outcome. Future experimenters will repeat reaction with copper (II) iodide.

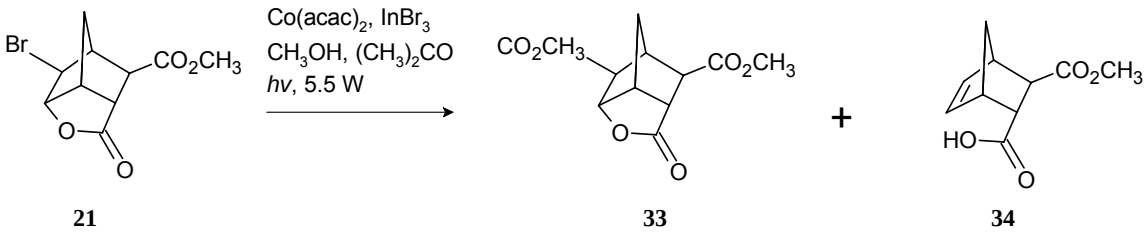
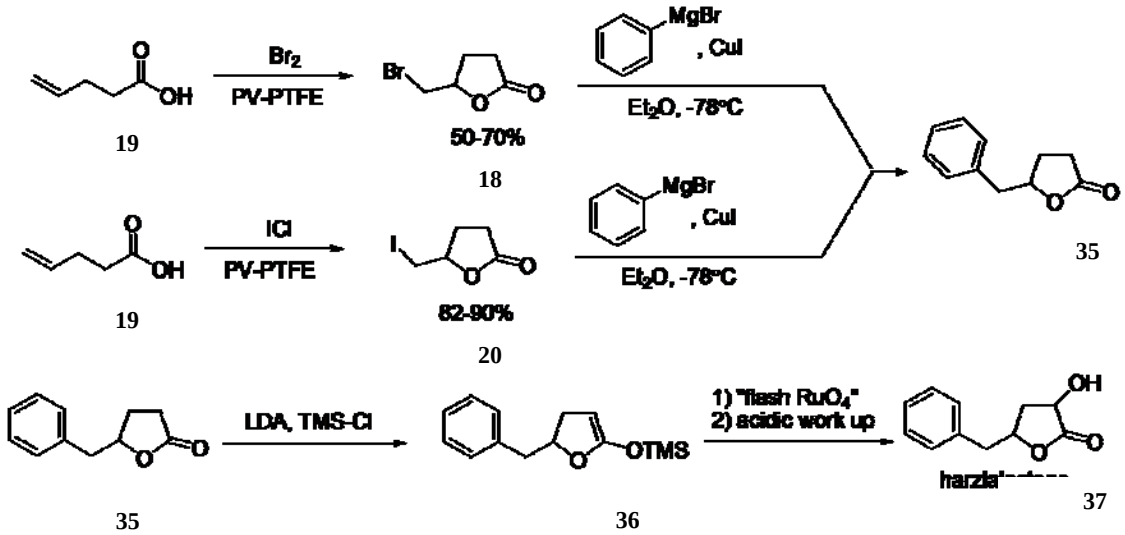


Figure 12. *Products of cobalt-catalyzed carbonylation of bromolactone* ***21*****.**

Figure 12 shows the products obtained from the cobalt-catalyzed reaction of bromolactone **21**. Bromolactone **21** was obtained from Olivia Smith because lactones that we had previously synthesized resulted in many impurities. Compound **34** was the major product of the reaction. Compound **33** was the desired product; however, it had only a 25% yield in the GC-MS, thus it was the minor product of the reaction. Compound **34** can be converted back into bromolactone **21** by treatment with bromine. Thus, repeating this procedure several times one can obtain a better overall yield of the desired ester **33**.



19 18 35 19 20 35 36 37

Figure 13. *Flash ruthenium tetroxide oxidation of compound* ***35***

Future research will include the synthesis of paraconic acids using flash ruthenium tetroxide (Figure 13). Ruthenium tetroxide (RuO_4) is a vigorous oxidating agent. Compared to more commonly used oxidating agents, such as permanganate, ozone or chromate, RuO_4 oxidizes faster and more selectively. Furthermore, RuO_4 can be used under milder reaction conditions.[25] Compound **35** will be treated with lithium diisopropyl amide (LDA), which is a strong base use to generate enolate ions. The enolate ion will then act as a nucleophile in a bimolecular nucleophilic substitution (S_N2) reaction with trimethylsilyl [$(CH_3)_3Si$-] (TMS) to form compound **36**. In a similar manner to above, a flash ruthenium tetroxide oxidation will be done on compound **36** in order to synthesize paraconic acid **37**.

CONCLUSION

The halactonization of alkenoic acids using PV-PTFE reactions proved to be more successful with iodine monochloride instead of bromine. Although the use of water as a

solvent for halolactonization of alkenoic acids gave higher yields and purity, more research needs to be done in order to further optimize reaction conditions. Cobalt-catalyzed photolytic carbonylation of halolactones gave us a desired paraconic acid precursor; however, in a low GC-MS yield. Future experimenters will have to focus on improving reaction conditions in order to improve the overall conversion of lactone into the corresponding methyl ester.

PV-PTFE reactions not only allowed us to successfully synthesize precursors to paraconic acids, but also enabled us to introduce "real" chemistry to undergraduate organic chemistry students. Through our application of PV-PTFE reactions, students realized that "real" chemical reactions are often more complex compared to idealized examples presented in the textbooks and are accompanied by side reactions and formation of byproducts. Furthermore, students were introduced to chemical literature and allowed to compare information obtained from various sources in order to evaluate it based on their experimental results.

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APPENDIX

GC-MS Data

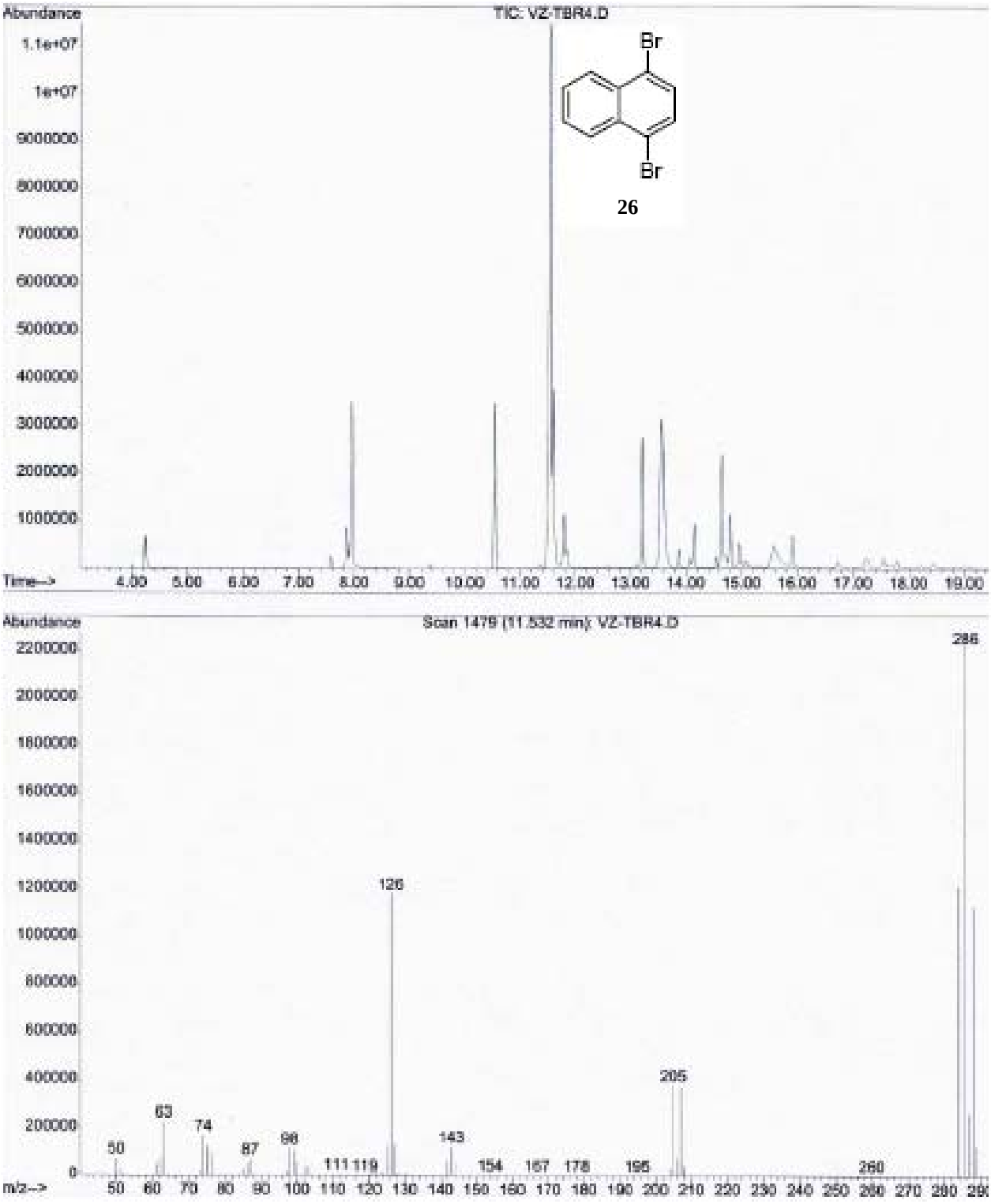

Figure 14. *GC-MS of 1,4-dibromonaphthalene*

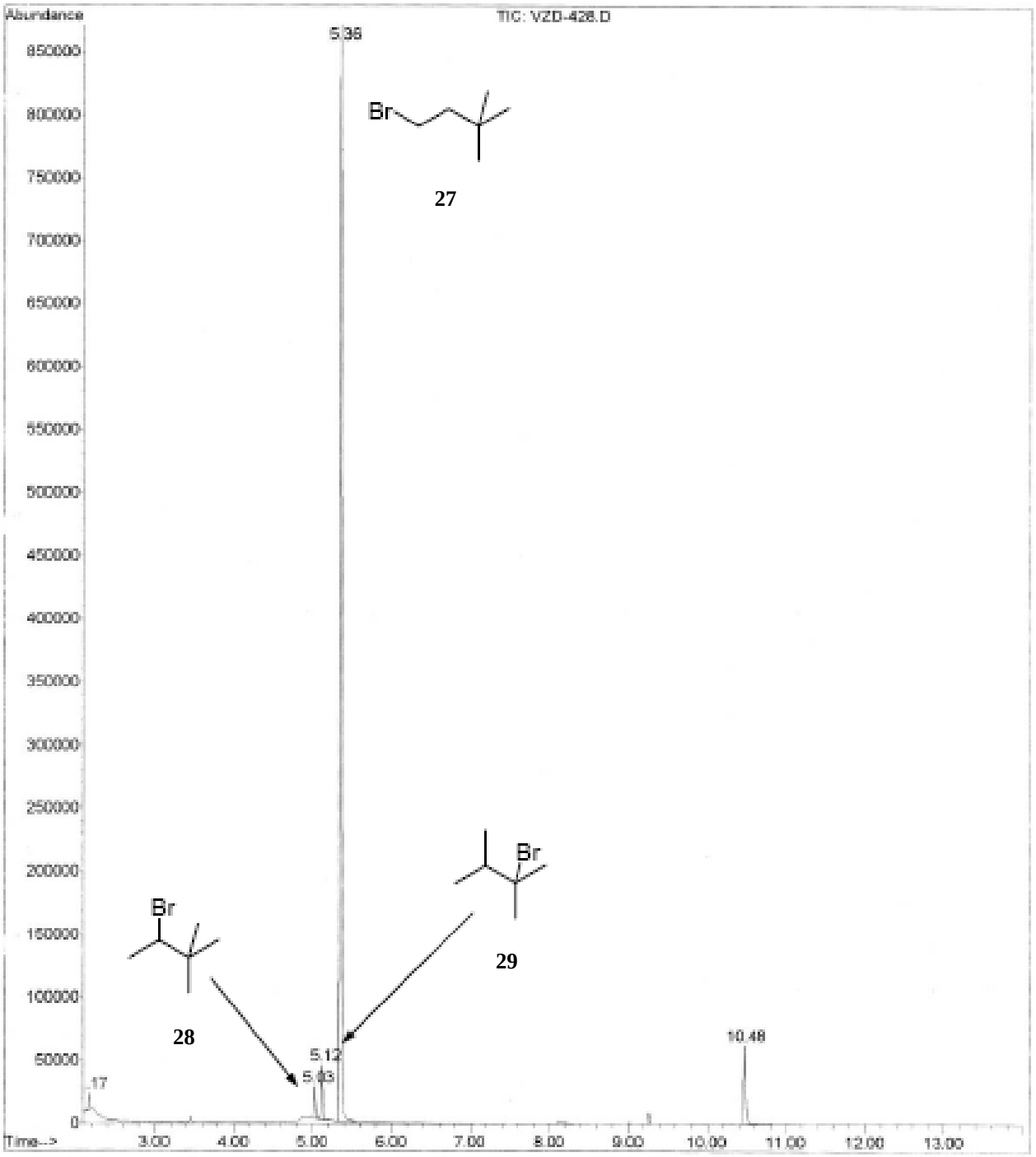

Figure 15. *Addition of HBr to 3,3-dibromo-1-butene in dichloromethane*

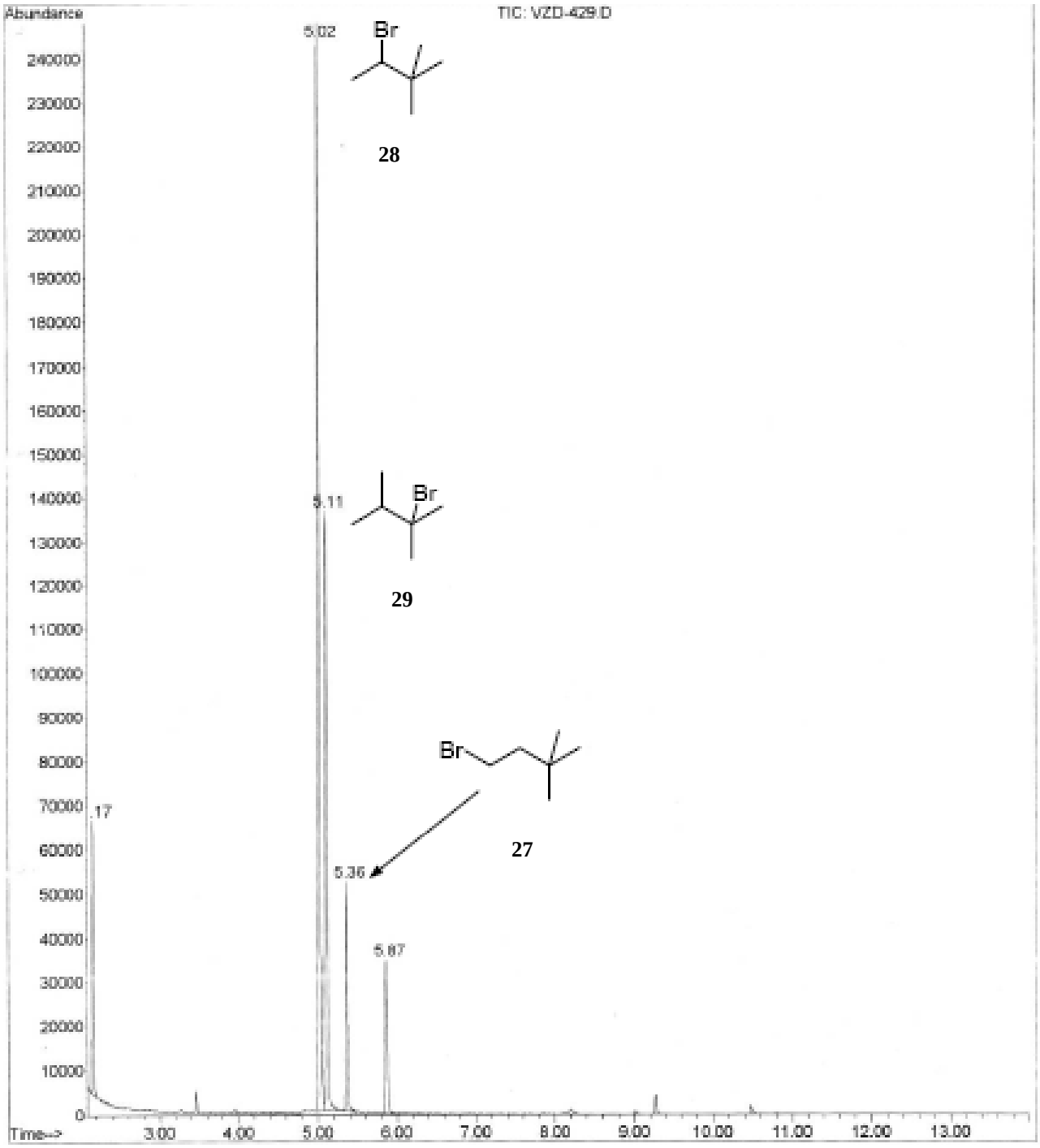

Figure 16. *Addition of HBr to 3,3-dibromo-1-butene in acetic acid.*

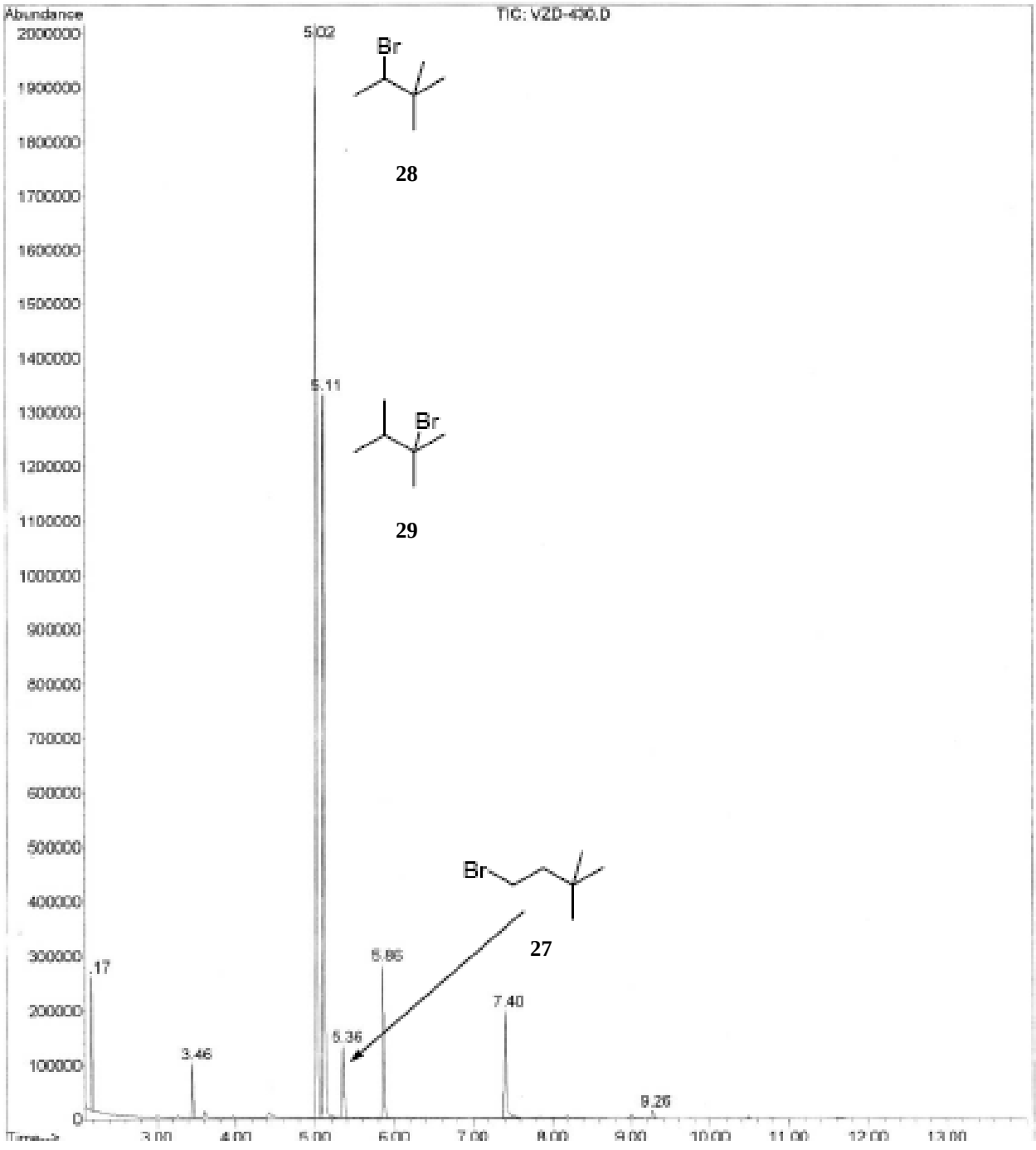

Figure 17. *Addition of HBr to 3,3-dibromo-1-butene in acetic acid with addition of zinc.*

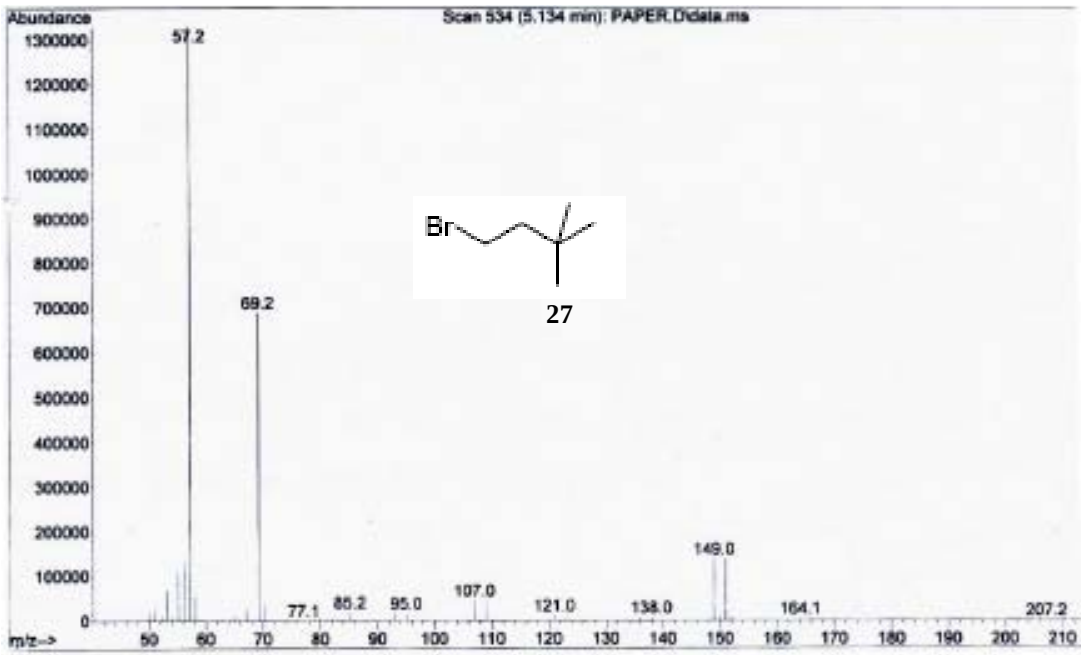

Figure 18. *Mass spectrum of 1-bromo-3,3-dimethylbutene (**27**).*

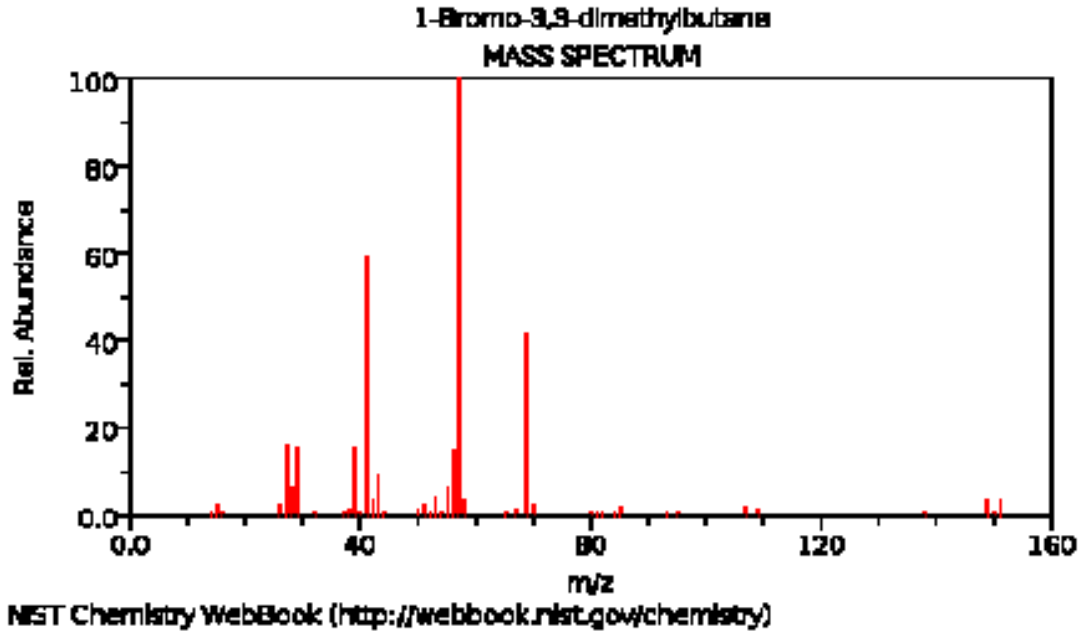

Figure 19. *Mass spectrum of 1-bromo-3,3-dimethylbutene (**27**) from NIST database.*

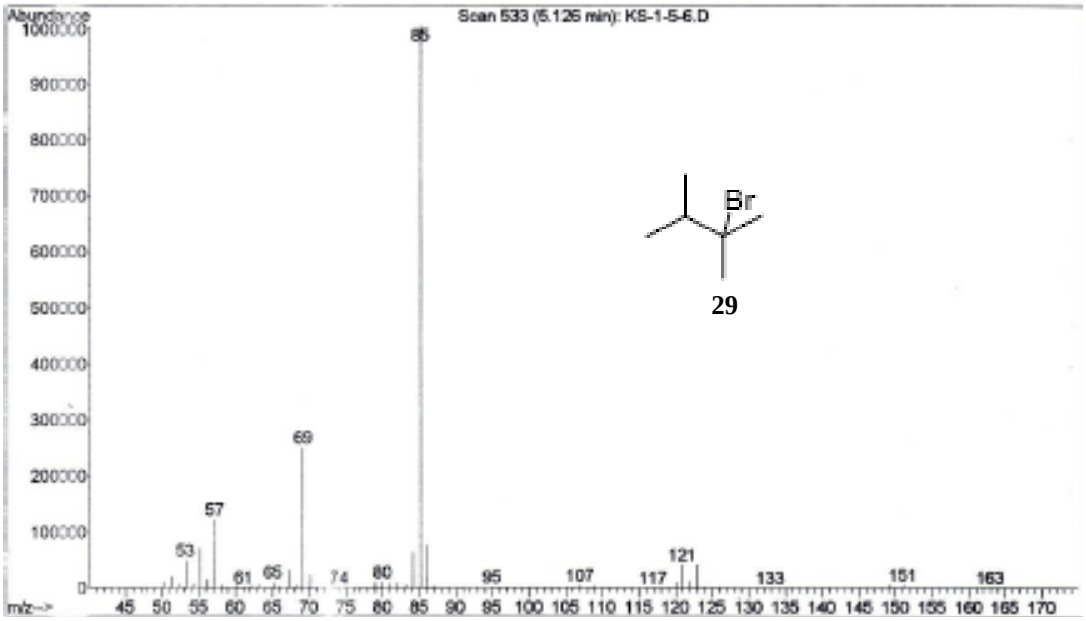

Figure 20. *Mass spectrum of 2-bromo-2,3-dimethylbutene (**29**).*

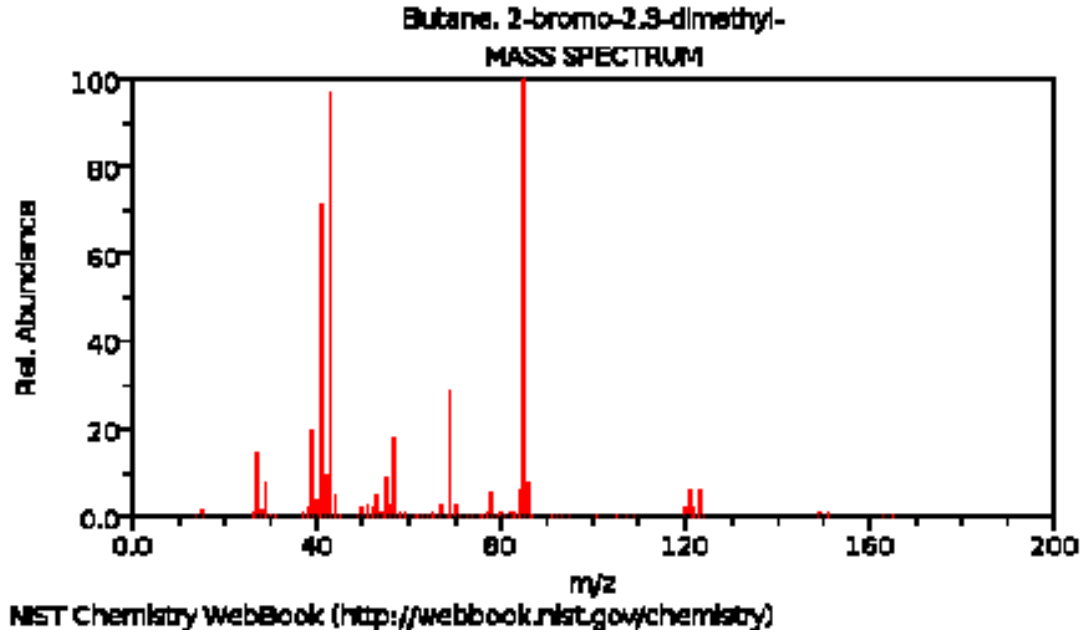

Figure 21. *Mass spectrum of 2-bromo-2,3-dimethylbutene (**29**) from NIST database.*

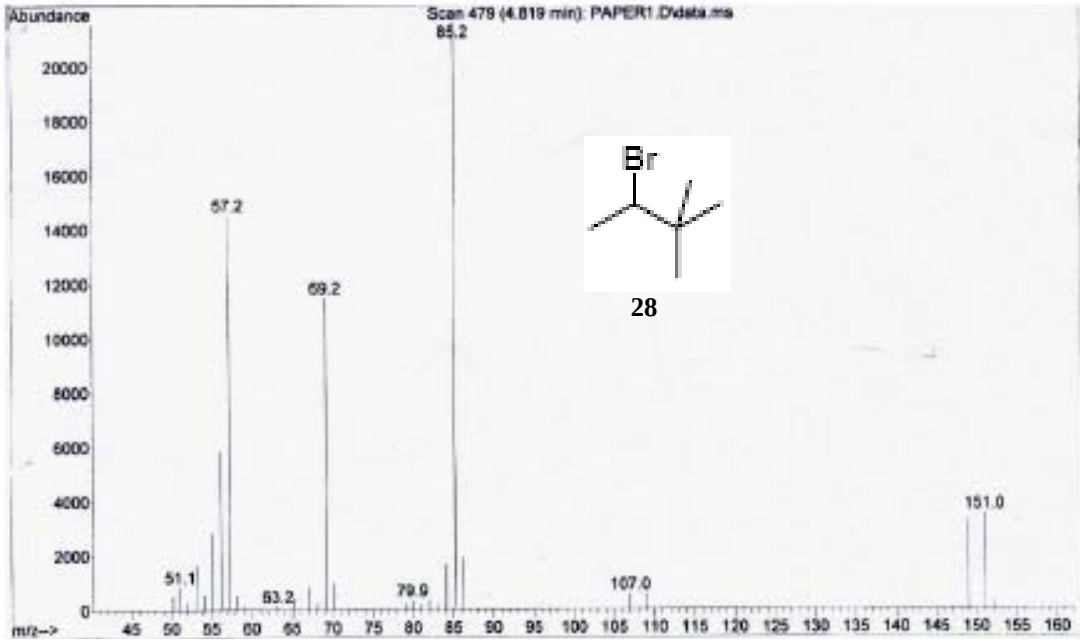

Figure 22. *Mass spectrum of 2-bromo-3,3-dimethylbutene (**29**).*

We did not find mass spectrum of 2-bromo-3,3-dimethylbutane in any of the databases. The spectrum above is in agreement with the reported data (Paradisi, C.; Bunnett, J.F.; Eck, D.L. *J. Org. Chem.*, **1980**, *45* (12), 2506–2507, **DOI:** 10.1021/jo01300a049): m/e M (164, 166) absent, 151, 149, 109, 107, 85, 69, 57, 41.