JOURNAL OF CHEMICAL EDUCATION

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Laboratory Experiment

Adapting Chiral Gas Chromatography into Existing Undergraduate Laboratories to Emphasize the Importance of Stereochemistry

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Cite This: J. Chem. Educ. 2024, 101, 547−553

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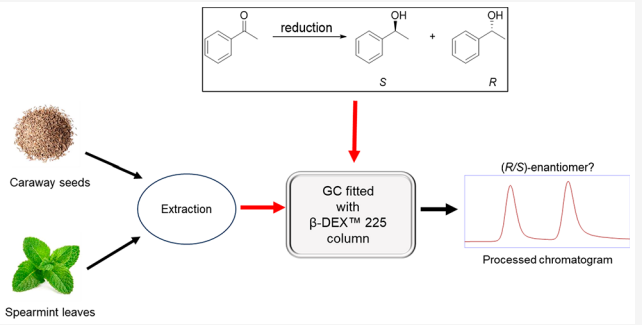
ABSTRACT: Owing to the critical role of stereochemistry in biotechnology, medicine, and industry, it must be well represented in undergraduate lab curricula. To achieve these stereochemical laboratory requirements without sacrificing existing lab techniques, we modified two standard laboratory experiments to include chiral GC analysis as follows. (1) The extraction of carvone from spearmint leaves and caraway seeds via steam-distillation or other extraction methods is widely used in laboratories for analyzing the stereochemistry of the extracted products. The experiment was modified to include a GC method using a β-DEX 225 column. This allowed the students to compare the retention times of the spearmint and caraway extracts with those in a racemic mixture and predict their stereochemical configurations (R or S). (2) The reduction of aldehydes and ketones is another common experiment performed at most institutions. Reduction of acetophenone using sodium borohydride produces a racemic mixture that is observed in the form of two retention times on the chromatogram. Alternatively, reduction using either enantiomer of commercially available Corey−Bakshi−Shibata (CBS) catalysts provides alcohols with higher enantiopurity. Using the GC data, students determined the dominant alcohol enantiomer produced by comparing the retention times of the product enantiomers with that of commercially available enantiopure alcohols. They also used chromatographic data to calculate the enantiomeric excess from their reactions. The experiments also teach students other essential methods, such as inert-atmosphere techniques, thin-layer chromatography, multivendor software analysis, and determining the effects of reaction conditions on product yield and stereochemistry.



KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Asymmetric Synthesis, Chirality/Optical Activity, Enantiomers, Gas Chromatography, Stereochemistry*

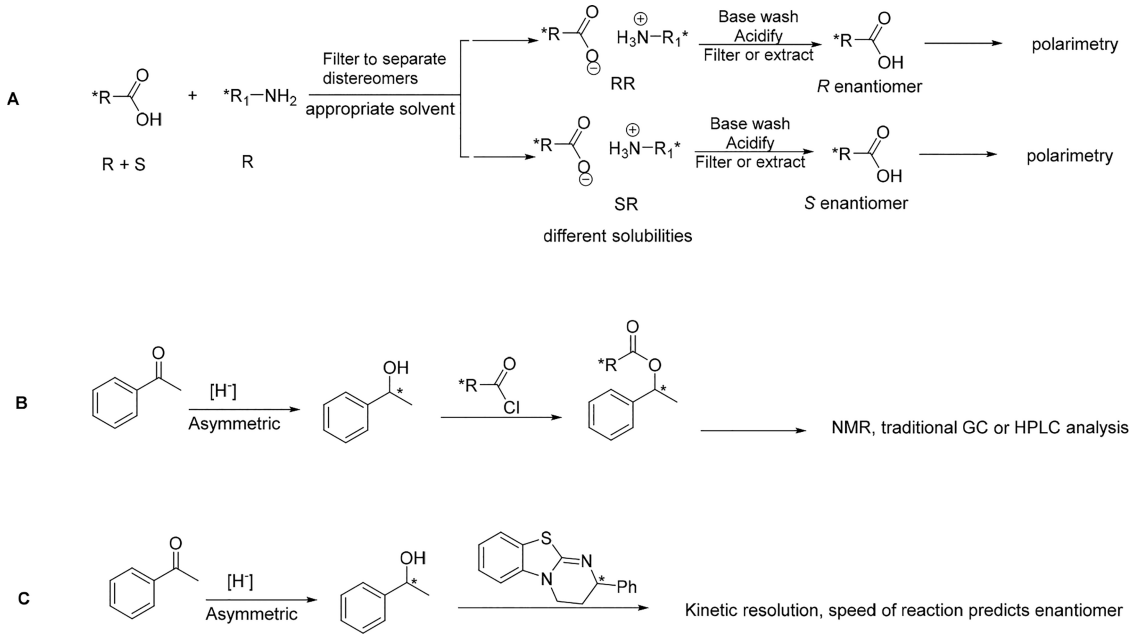
INTRODUCTION

The incidence of the thalidomide tragedy,[1] as well as the development and commercialization of drugs like ibuprofen[2] and naproxen,[3] where only one enantiomer is bioactive while the other is either inactive or toxic, have elicited additional emphasis on stereochemistry in STEM education. The methods for determining the absolute configurations of chiral molecules described and used in most undergraduate curricula rely either on acid−base resolution[2,4,5] or on determining diastereomeric ratios of chiral derivatives using common separation and spectroscopic techniques (Scheme 1). In acid−base resolution, a racemic carboxylic acid reacts with an enantiopure amine to form diastereomeric salts that can be easily separated based on their physical properties, the most common of which is solubility.[5,6] The salts are separated, washed with a basic solution, reacidified to form enantioenriched acids, and filtered or extracted using an organic solvent. The enantioenriched acids are then analyzed using polarimetry. This method can also separate racemic amines using enantiopure acids but is limited to molecules with acidic and amine functional groups. Experiments involving the analysis of chiral molecular derivatives using NMR or traditional GC and HPLC typically span one or two 3−4 h lab periods of synthesis and purification, followed by one or two 3−4 h lab periods of chiral derivatization and possible purification before analysis.[7−11] This method is best suited for multiweek laboratory projects; notably, chiral derivatizing agents are costly single-use chemicals. Recently, King and co-workers reported an experiment where an enantioenriched alcohol was synthesized in the first week and then reacted with an enantiomer of homobenzotetramisole.[12] The reaction rate, determined via TLC analysis, was then used to predict the dominant enantiomer of the alcohol. While this is a promising

Received: May 9, 2023
Revised: December 17, 2023
Accepted: January 5, 2024
Published: January 30, 2024

https://doi.org/10.1021/acs.jchemed.3c00416
J. Chem. Educ. 2024, 101, 547−553

Scheme 1. Existing Laboratory Experiments to Demonstrate Stereochemistry[a]



[a](A) General scheme for the acid−base resolution of carboxylic acids and amines followed by polarimetry; (B) representative scheme for asymmetric synthesis followed by chiral derivatization and analysis; and (C) asymmetric reduction followed by kinetic resolution to predict the enantiomers.

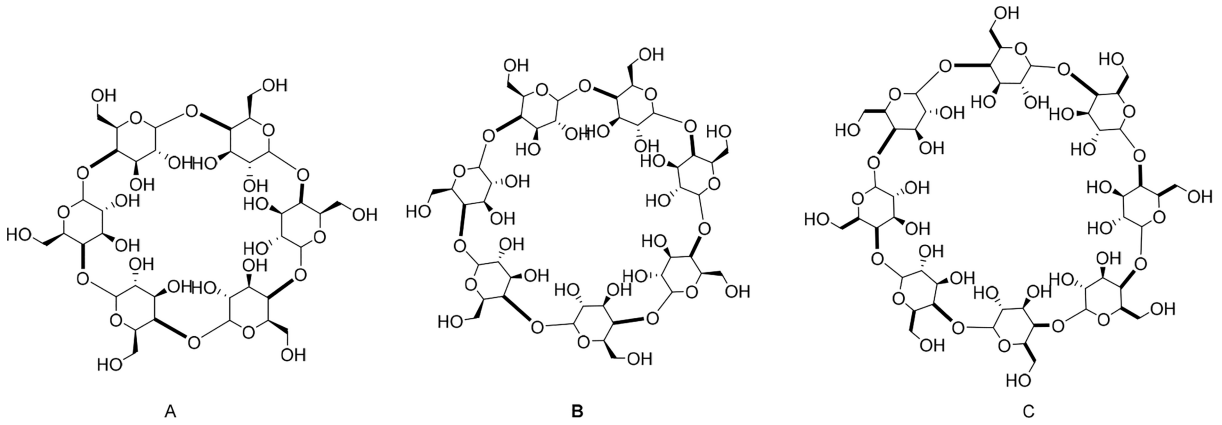


Figure 1. Structures of α (A), β (B), and γ (C) cyclodextrins.

experiment, it only predicts the most abundant enantiomer, not the enantiomeric ratio, and requires a minimum of two 3−4 h sessions of laboratory experiments.

Both the chiral derivative analysis and kinetic resolution experiments could be completed in a single 3−4 h lab session with the addition of an appropriate chiral GC method. GC and HPLC using chiral columns are common in industry and academia for analyzing enantiomers and determining enantiomeric ratios.[13−15] A chiral column has a chiral stationary phase, which under the right GC conditions, will have a higher affinity for one enantiomer over the other, resulting in different observable retention times (RT), for both enantiomers. The commonly used categories of chiral stationary phases are (1) amino acid derivatives such as Chirasil Val, (2) metal−analyte complexes such as bis [(1*R*)-3-(heptafluorobutyryl)-camphorate]-Ni^{2+} complex and bis(*L*-hydroxyprolinato)-copper(II) complex, and (3) carbohydrate derivatives such as cyclodextrins.[16−18] The three commonly used cyclodextrins, α, β, and γ (Figure 1), function based on the following analyte−cyclodextrin interactions: size inclusion, dipole−dipole interactions, hydrophobic interactions, hydrogen bonding, cyclodextrin capping, and steric interactions.[19−21]

Herein, we describe how including a GC device fitted with the cyclodextrin column β-DEX 225 in two undergraduate organic chemistry experiments, along with the subsequent GC data analysis using MNova, enables a better student experience in terms of understanding: (1) how two sources of carvone can produce different isomers; and (2) how asymmetrically reducing acetophenone with a Corey−Bakshi−Shibata catalyst, specifically (*R*/*S*)-2-Methyl-CBS-oxazaborolidine (CBS) produces an excess of one enantiomer compared with the uncatalyzed reaction that produces a racemic alcohol mixture. The carvone experiment was completed in a single 4-h laboratory session, whereas the reduction experiment required two 4-h sessions. The experiments also demonstrate other common organic chemistry techniques.

https://doi.org/10.1021/acs.jchemed.3c00416
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HAZARDS

Diethyl ether, tetrahydrofuran, ethyl acetate, hexane, and methanol are highly flammable volatile organic solvents. Acetophenone and 1-phenylethanol are flammable and severe eye irritants. All flammable solvents were kept away from an open flame. The CBS catalyst and borane dimethylsulfide complex (BMS) are flammable and moisture-sensitive. If placed in contact with water, they produce a flammable gas that ignites spontaneously. 9-Borabicyclo[3.3.1]nonane (9-BBN) solution is flammable, toxic, and moisture sensitive. 3 M HCl solutions are corrosive. Gloves and eye protection were mandatory, and all parts of the experiments were performed in a fume hood.

Needles were handled under the strict supervision of the instructor and TAs. Used short needles were returned to TAs immediately after use. Long reusable needles were cleaned using the cleaning apparatus immediately after use and kept in an oven.

THE NATURAL PRODUCT EXTRACTION

The presence and olfactory properties of carvone in spearmint leaves and caraway seeds are commonly used in organic chemistry to demonstrate the impact of chirality.[22−28] Although carvone is the major component in the oils of both caraway and spearmint extracts, these sources provide different enantiomers of this compound. The spearmint extract contains (*R*)-carvone, which imparts a minty odor, whereas the caraway extract contains (*S*)-carvone, which imparts an earthy musk odor (Figure 2).[26] Consequently, spearmint leaf and caraway seed extracts are commonly used in undergraduate laboratories to demonstrate natural product extraction and stereochemistry.

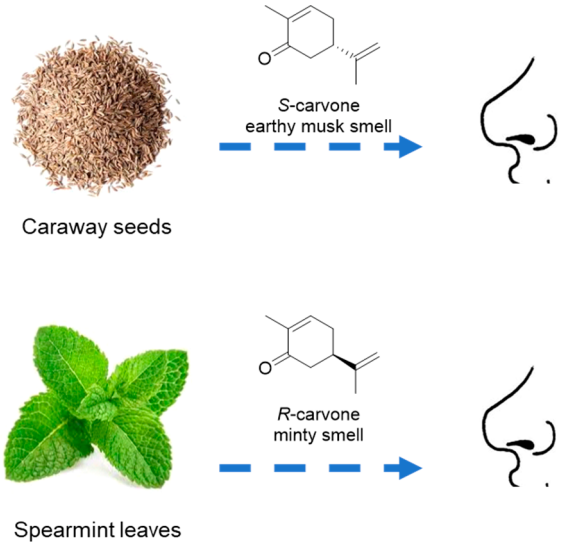

Figure 2. Spearmint leaves and caraway seeds produce different enantiomers of carvone.

Experimental Overview

This experiment was performed in a first-semester organic chemistry laboratory class. Students worked in groups of four, with each group further divided into two pairs. One pair extracted carvone from spearmint leaves, while the other extracted it from caraway seeds. The experiment's goals were to extract carvone from spearmint leaves and caraway seeds and use chiral GC and MNova to assign R/S classifications to the carvone extracts from both sources.

GC Data Analysis

Data analysis was performed using the MNova software. Data from the commercial (*R*)-enantiomer and a racemic carvone mixture were provided to each student. Thus, each group analyzed four data sets, which included data from commercially obtained (*R*)-carvone, a racemic mixture of carvone, the spearmint extract from that team, and the caraway seed extract from the other team. The (*R*)-enantiomer and racemic mixture data were used to identify the RTs of the (*R*)- and (*S*)-enantiomers. The RTs from the extract data were then matched with the correct enantiomers (Figure 3).

REDUCTION OF ACETOPHENONE

Reducing aldehydes and ketones to produce primary and secondary alcohols is a fundamental organic synthetic methodology in most undergraduate organic chemistry laboratory curricula. The purpose of the reduction laboratory experiments described in this manuscript are (1) to apply the synthetic and analytical techniques taught in that semester in a single organic synthesis experiment and (2) to use chiral GC and MNova to identify the products as (*R*)- or (*S*)-enantiomers and calculate the enantiomeric excess of the asymmetrically synthesized products.

Acetophenone reduction using CBS in the presence of BMS is also part of King's synthesis and kinetic resolution laboratory experiment.[12] Although acetophenone reduction by sodium borohydride (Scheme 2) has been a part of our laboratory curriculum at Bridgewater College for over two decades, it was modified two years ago to include an additional week of asymmetric reduction and GC analysis. In the first year, it was part of a two-week laboratory experiment involving symmetric reduction using sodium borohydride. In the second year, the symmetric reduction was performed using 9-BBN, allowing an additional week for the column chromatographic purification of the 1-phenylethanol product and cyclooctanediol byproduct. Thus, a three-week experiment comprising 1 week of reduction using 9-BBN, 1 week of product purification, and 1 week of CBS-catalyzed reduction and GC analysis provided the experience of a typical organic synthesis experiment.

Asymmetric Reduction

Acetophenone was reduced using (*R*)- or (*S*)- CBS catalyst and borane (BMS) reagent (Scheme 3). The concepts and available methods of asymmetric synthesis and analysis were covered in a lecture delivered prior to the experiment. The students were instructed to determine the enantiomers produced by each catalyst and calculate the enantiomeric excess of the dominant enantiomer. To achieve this, they had to pick peaks at the specific RTs corresponding to the enantiomers and manually integrate them using MNova. Thus, after integration, the percentages of the enantiomers observed in the plot were directly related to the enantiomeric excess (ee) of the product as follows: ee = % of the enantiomer with the highest integral − % of the enantiomer with the lowest integral. A short video demonstration of the opening and analysis of the FID files was provided to students.

GC Data Analysis

The GC data from the reduction experiment were analyzed using MNova. Again, each group analyzed four data sets, including data from a commercially obtained (*S*)-enantiomer

https://doi.org/10.1021/acs.jchemed.3c00416
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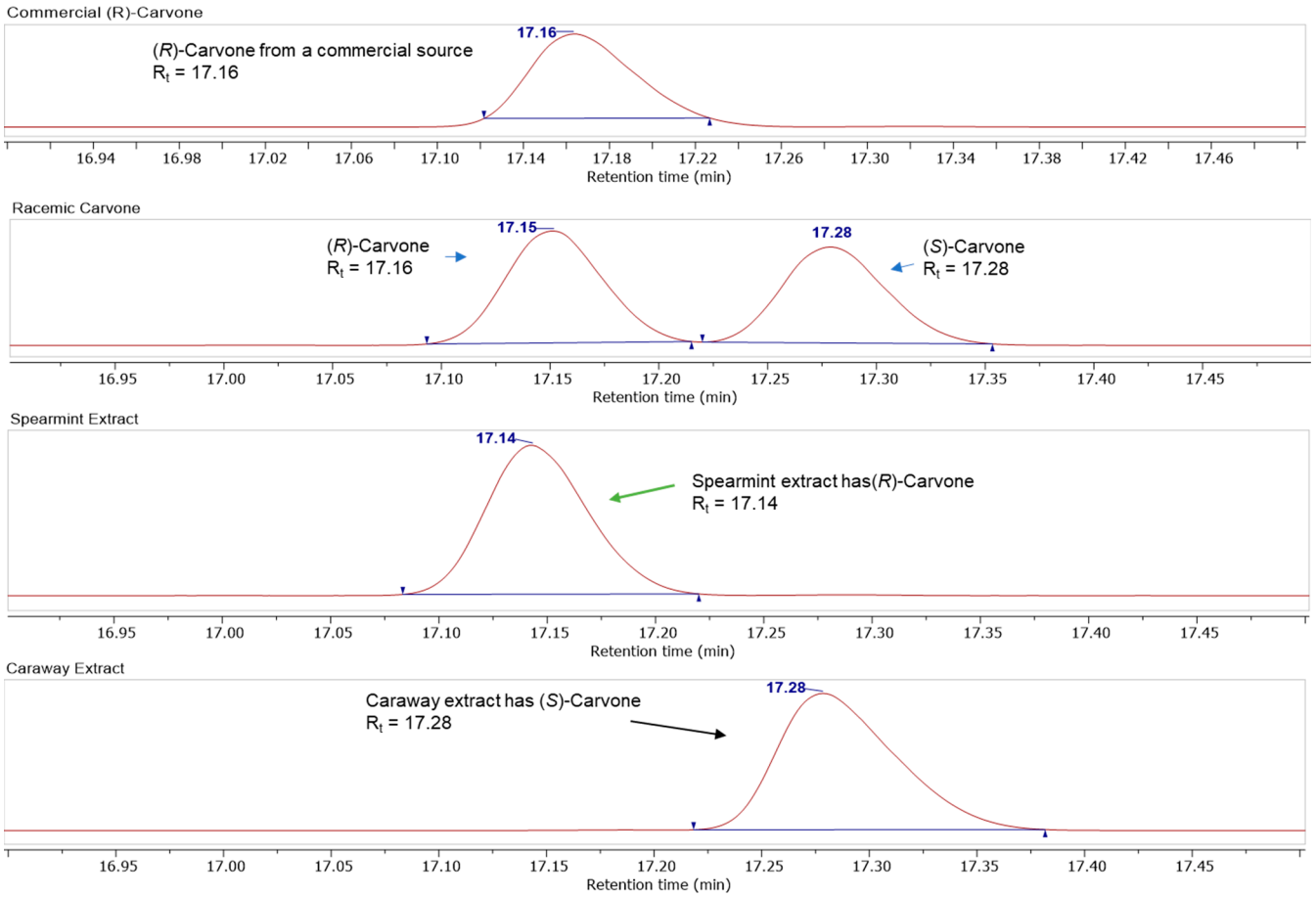
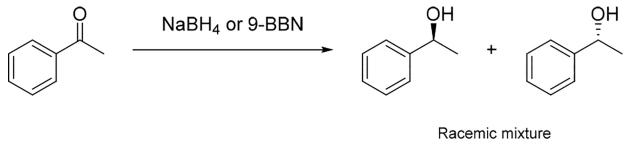
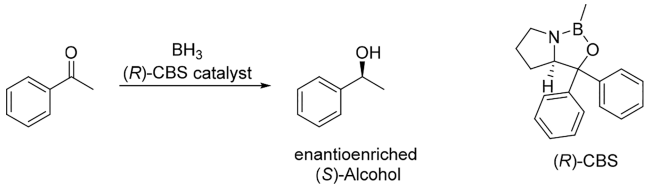


Figure 3. Comparative GC analysis of commercial (*R*)-carvone, a racemic carvone mixture, and the student-obtained spearmint and caraway extracts. The spectra show that both extracts comprised different enantiomers of carvone.

Scheme 2. Reduction of Acetophenone to Produce Racemic Alcohol Products



Scheme 3. Asymmetric Reduction of Acetophenone



of 1-phenylethanol, sodium borohydride or the racemic 9-BBN reduced product, the (*R*)-CBS-catalyzed reduction, and the (*S*)-CBS-catalyzed reduction. The (*S*)-enantiomer and symmetric reduction data were used to designate the RTs of the (*R*)- and (*S*)-enantiomers. These were then used to identify the correct enantiomers of 1-phenylethanol (Figure 4).

DISCUSSION

The stereochemistry class began with viewing and discussing a 30 min video documentary by the New York Times on the thalidomide tragedy.[29] Subsequently, the students were taught the impact of stereochemistry, including a discussion on carvone. The natural product extraction experiments were timed to occur at the same time.

The first-semester lab course included 6 weeks of learning the techniques and 3 weeks of applying the techniques through synthesis. The students were required to write summative conclusions in their notebooks for the technical aspects of the course. With the synthesis experiments, they used stereochemical assignments, yields, and other spectroscopic data to write publication-style reports in addition to notebook entries. This included the reduction lab, which was the final laboratory course of the semester. The ten pairs of students who performed the CBS-catalyzed reduction experiment obtained 14%−100% yields with ee ranging between 70 and 99.9%. The variations in yields and ee by the various groups led to meaningful discussions about how minor changes in reaction conditions such as ice bath temperatures above 6 °C, speed of addition of the acetophenone solution or concentration of acetophenone solution added to the reaction mixture could lead to variations in the ee.

As with other science laboratories, the experiments described herein have a 2-fold purpose; first to help students develop practical laboratory skills and techniques and second, to reinforce concepts learned in class. In the case of the extraction experiment, the primary concept being supported was stereochemistry, while the reduction lab reinforces multiple concepts, including stereochemistry. In our organic chemistry laboratories, we have moved away from the

https://doi.org/10.1021/acs.jchemed.3c00416
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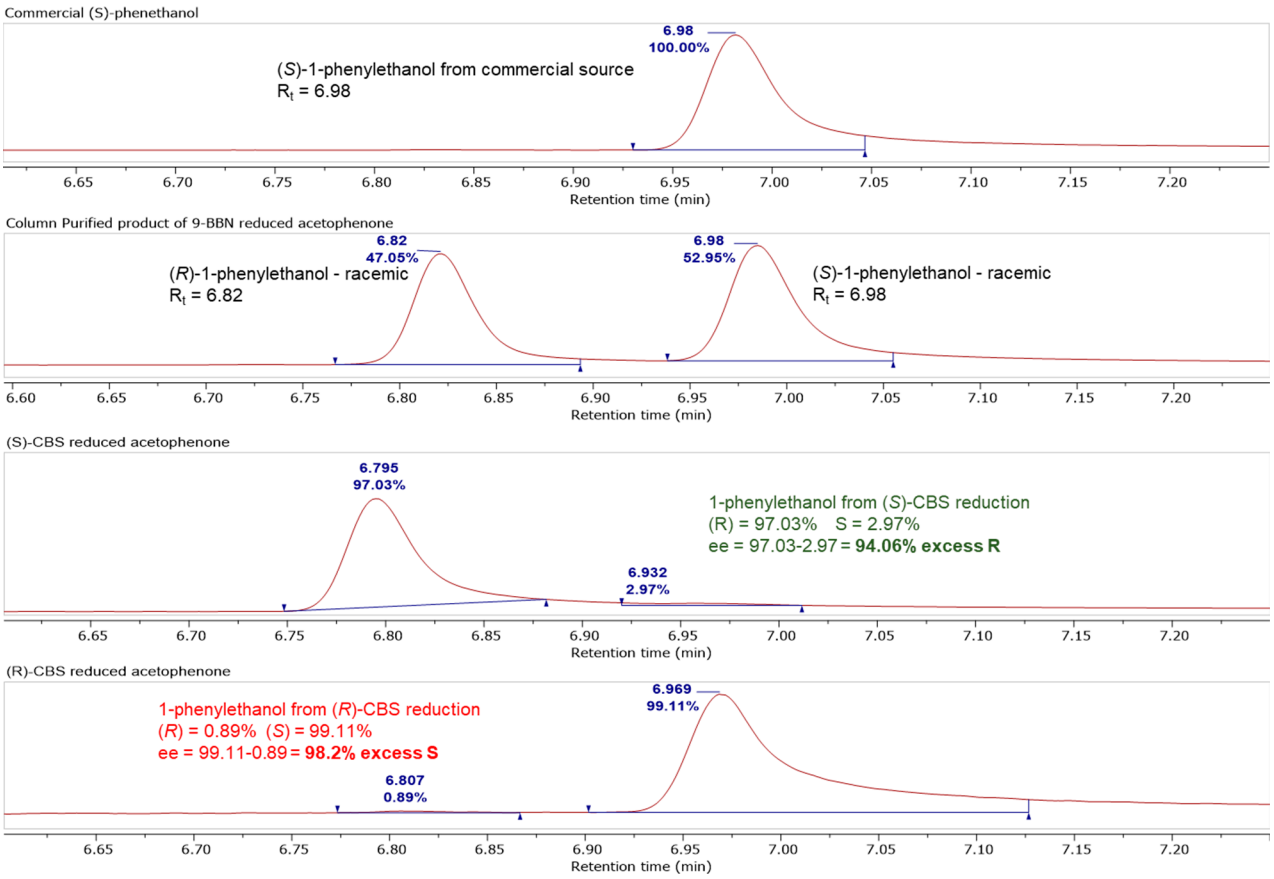

Figure 4. GC Analysis of 9-BBN reduction and CBS-catalyzed reductions, with a sample of purchased pure (*S*)-enantiomer.

traditional prelab and postlab quiz system to where students incorporate the answers as part of their prelab predictions and postlab discussion/conclusions in their notebooks. Thus, for the extraction lab, all students who did these experiments correctly ranked the components of the oils limonene, carvone, and carveol in increasing order of polarity and indicated their expected relative positions on the TLC plate in their notebooks before coming to the lab. They also stated that they expected similar components in either extract to show at the same spot since they have the same polarity irrespective of whether enantiomers. All students could derive the stereochemistry-related conclusions in their notebooks and reports for both experiments using data from the GC. Overall, both laboratory experiments provided a meaningful foundation for understanding stereochemistry, GC, and other techniques.

An anonymous postlab survey was also administered to measure the impact of both laboratories on GC technique training and reinforcement of stereochemistry concepts. The survey was issued 2 weeks after the reduction lab. No personal information was requested or collected. Nineteen students accepted the invitation to participate in the survey. A 3-point, 5-point Likert scale and short response questions were used to assess the students' appreciation. The students were encouraged to take the full survey at a sitting and to not refer to any textbook, the Internet or any other resources while answering the questions.

Survey Questions and Statements

1. How does gas chromatography differ from thin-layer chromatography as applied in spearmint extraction and ketone reduction laboratories?
2. Based on your recollection of the prelab lecture from the reduction lab, what is the difference between the regular GC we used during fractional distillation at the early stage of the semester and the chiral GC used for the extraction and asymmetric reduction lab?
3. Before the spearmint/caraway extraction lab, how do you gauge your knowledge about carvone and the fact that extract from both spearmint and caraway sources have the same molecule but different isomers?
4. The spearmint/caraway extraction lab helped you to better appreciate the fact that both extractions have the same principal chemical component but different smells because they are different enantiomers.
5. The data from the chiral GC contributed greatly to your understanding of the enantiomers in the spearmint/caraway extraction experiment?
6. Write a short comment on why you chose your answer to the question above. Include any suggestions for future improvements of the experiment.
7. Cast your mind to our class section on enantiomers and the video documentary you watched on the thalidomide problems and choose the appropriate response to the following statement. There is an immense need for asymmetric synthesis.
8. List the various ways by which asymmetric induction can be achieved.
9. The asymmetric reduction of acetophenone using the CBS-catalyst and the subsequent analysis using the chiral GC helped you to better understand the use of catalysts for asymmetric synthesis.

https://doi.org/10.1021/acs.jchemed.3c00416
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Table 1. Summary of Survey Responses

	number of respondents (n = 19)				
question statement	strongly agree	agree	neither agree nor disagree	disagree	strongly disagree
4	7 (36.8%)	10 (52.6%)	2 (10.5%)	0	0
5	8 (42.1%)	10 (52.6%)	0	1 (5.3%)	0
7	13 (68.4%)	2 (10.5%)	4 (21.1%)	0	0
9	9 (47.4%)	6 (31.6%)	3 (15.8%)	1(5.3%)	0
10	10 (52.6%)	8 (42.1%)	1 (5.3%)	0	0

10. The use of chiral GC and MNova contributed to your understanding of asymmetric reactions and enantiomeric excess in the reduction experiment.
11. Briefly explain how the all the techniques we used in the extraction and reduction laboratories including TLC, MNova, and GC helped you understand enantiomers. You may refer to the conclusions you made in your lab notebook for help.

In a three-point question, students were asked to rate their knowledge that despite the difference in smells, the major components of spearmint and caraway oils are different isomers of the same molecule. This fact was mentioned in the lecture in the week of the extraction lab. Ten respondents (52.6%) remembered from class, with another one (5.3%) seeing it somewhere, while eight respondents (42.1%) reported not knowing. In a follow-up to that question using a 5-point Likert scale, 17 students (89.4%) either strongly agreed or agreed that the extraction lab coupled with chiral GC helped them to appreciate that fact better. Two students (10.5%) neither agreed nor disagreed.

Furthermore, for either experiment, only one respondent (5.3%) disagreed that data from the GC helped them to better understand enantiomers, with the remaining 18 respondents (94.7%) either strongly agreeing or agreeing. Fifteen respondents (78.9%) agreed that the combination of CBS-catalyzed reduction of acetophenone and chiral GC analysis helped them better understand the use of catalysts for asymmetric inductions. Three respondents (15.8%) neither agreed nor disagreed, and one (5.3%) disagreed.

A summary of the responses from the five-point Likert statements is provided in the table below (Table 1).

Below are listed a few student comments on the laboratory course in response to the question, "Briefly explain how all the techniques we used in the extraction and reduction laboratories including TLC, Mnova, and GC helped you understand enantiomers. You may refer to the conclusions you made in your lab notebook for help."

- "Mestrenova and GC were very important because they allowed me to visualize exactly what enantiomer I was looking at. I think this helps with making real world connections to things such as thalidomide. TLC is important for tracking the progress of the reaction and gives us a quick idea of if the product has been collected or not without running extensive tests."
- "We were able to compare GC of one commercial enantiomer to either a racemic mixture of both or an isolated enantiomer from our own experiment, which allowed us to determine which enantiomers were which as well as how much of each were obtained. Mestrenova helps visual this graphically and TLC allowed us to see the different functional groups in the compound, helping to confirm whether or not our desired product was formed."
- "They all helped understand the steps it takes to verify which organic compounds were enantiomers of each other."

CONCLUSIONS

Two common organic chemistry laboratory experiments, (1) spearmint/caraway oil extraction and (2) the reduction of acetophenone, were modified by adding appropriate chiral gas chromatography methods. Adding the methods to these experiments exposed students to chiral GC techniques and applications and helped to further emphasize stereochemical concepts and applications taught in class. In the extraction of carvone from spearmint leaves and caraway seeds, students compared data from analysis of their extracts and solutions of commercially available relatively enantiopure carvone to assign (*R*)- and (*S*)-designations to their extracts. With additional data from TLC, they concluded that carvone extracts from spearmint leaves are enantiomers of carvone extracts from caraway seeds, even though they are from different sources and smell different. For the reduction lab, students assigned (*R*)- and (*S*)-designations and calculated enantiomeric excess of their enantioenriched products using the GC data.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.3c00416.

Example brief descriptions with file formats indicated are shown below; customize for your material (PDF)

Example brief descriptions with file formats indicated are shown below; customize for your material (DOCX)

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https://doi.org/10.1021/acs.jchemed.3c00416
J. Chem. Educ. 2024, 101, 547−553

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding for this project was provided by the Department of Chemistry and Biochemistry's internal funds and Bridgewater College's Faculty Research grant (15-016249-63501). The authors are grateful to Dr. Joseph Crockett for his pioneering work.

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