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Cover Page Footnote

Steven P. Bondi, FCRH 2011, is from New Hyde Park, New York. He is a mathematics major and a chemistry minor. Steven is currently conducting organic chemistry research in Dr. Shahrokh Saba's lab on amine synthesis and alcohol enantiomeric ratio determination. After graduating, Steven will be attending medical school and pursuing a career in medicine.

NMR Determination of Enantiomeric Composition of Chiral Alcohols Using Camphorsulfonate Esters

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Introduction

Most biologically active compounds, including pharmaceuticals, have chiral molecular structures. With increased recognition that enantiomers of chiral drugs are metabolized differently, there has been enormous interest in the development of enantioselective methodologies for the synthesis of chiral compounds.

NMR spectroscopy has emerged as a powerful method for discrimination of enantiomers of chiral compounds.[1] One strategy by which the NMR method is exploited is based on converting the enantiomers of a chiral compound to diastereomers using a chiral derivatizing agent. These diastereomers often display anisochronous NMR signals, which can be identified and integrated affording quantitative measurements of the optical purity of a sample.

The hydroxyl group is a highly prevalent functionality found in naturally occurring compounds and pharmaceuticals. The chiral auxiliaries used in common practice to identify enantiomeric alcohols are usually chiral carboxylic acids, or their chlorides, which readily form diastereomeric esters and show appreciable diastereomeric differences at certain positions in the molecule. The most widely used carboxylic acid for such studies is that developed by Mosher, namely α-methoxy-α-trifluoromethylphenylacetic acid.[2] However, while commercially available, this compound is 173 times more expensive than (*S*)-camphorsulfonyl chloride [(*S*)-CSCl] (Figure 1).

A much older chiral auxiliary is camphorsulfonic acid, which has been used extensively to derivatize chiral amines, but not to make derivatives of chiral alcohols. It has not been extensively used to make derivatives of chiral alcohols. This is because sulfonate esters are more difficult to prepare than carboxylate esters. On the other hand, the poor reactivity of sulfonyl chlorides, as compared to carboxylic acid chlorides, makes this reagent more easily stored without decomposition by hydrolysis.

We have recently expanded the protocol for the hydration of 1-hexene, which affords 2- and 3-hexanols, by treating the reaction product with (*S*)-CSCl and triethylamine to produce diastereomeric esters of these chiral alcohols. ^{1}H and ^{13}C NMR spectroscopy were used to determine the enantiomeric composition of alcohols obtained.[3]

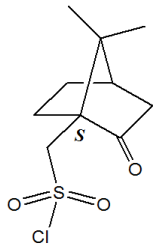

Figure 1

We have now extended our studies to other chiral alcohols and herein report on the synthesis and ^{1}H and ^{13}C NMR spectra of camphorsulfonate esters of (+/-)-ethyl-3-hydroxybutyrate, (+/-)-2-butanol, (+/-)-1-phenylethanol, (+/-)-2-hydroxymethyloxirane, and (+/-)-1-phenyl-2-propyn-1-ol.

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Experimental Procedure

A 50 mL Erlenmeyer flask was charged with an alcohol (5 mmol). To this, a solution of triethylamine (7.5 mmol) and methylene chloride (25 mL) was added. The mixture was swirled and cooled in an ice H_2O bath for 15 minutes. (1*S*)-(+)-Camphorsulfonyl chloride (5.5 mmol) was then added over a period of 5 minutes. The flask was then ice cooled for an additional 45 minutes. The product was then purified by sequential extractions of the reaction mixture with ice-cold H_2O (10 mL), 10% HCl (8 mL), a saturated $NaHCO_3$ solution (10 mL), and finally with H_2O (10 mL). The organic layer was then dried over anhydrous sodium sulfate, followed by rotary evaporation of the solvent affording the sulfonate esters in 75-86 percent yield.

Results and Discussion

The ^{1}H NMR spectrum of the camphorsulfonate (CS) ester derived from (*R*)-ethyl-3-hydroxybutyrate shows two doublets centered at 3.0 and 3.7 ppm, representing the diastereotopic hydrogens of the SCH_2 moiety. The diastereomeric CS esters derived from (+/-)-ethyl-3-hydroxybutyrate display four well-resolved doublets representing the same hydrogens in the two separate diastereomers (Figure 2). Addition of a small sample of the CS ester derived from authentic (*R*)-ethyl-3-hydroxybutyrate to that obtained from the racemic mixture lowers the intensity of the doublets centered at 3.1 and 3.6 ppm allowing complete assignment of the doublets to the individual diastereomers. The ^{13}C NMR spectrum of CS esters derived from (+/-)-ethyl-3-hydroxybutyrate shows separate peaks of equal intensity at 169.22 and 169.32 ppm for the ester carbonyl carbon of CS esters derived from the R and S enantiomers of ethyl-3-hydroxybutyrate respectively. Assignment of these peaks was made by adding a small sample of the CS ester derived from the R enantiomer of ethyl-3-hydroxybutyrate.

The ^{1}H NMR spectrum of the CS ester derived from authentic (*R*)-2-butanol similarly shows two separate doublets centered at 3.0 and 3.6 ppm for the SCH_2 moiety. For the CS diastereomers obtained from racemic 2-butanol, four doublets representing the same hydrogens are observed. Assignment of the signals was made by adding a small sample of CS ester of (*R*)-2-butanol (Figure 3). The ^{13}C NMR spectrum of CS diastereomers obtained from racemic 2-butanol, shows partially resolved signals for the carbon attached to the oxygen in the 2-butyl moiety. Assignment of the signals was made by adding a small sample of CS ester of (*R*)-2-butanol.

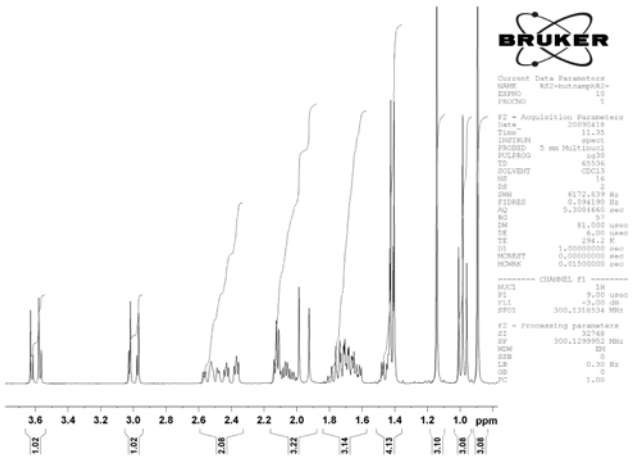

Figure 3

The ^{1}H NMR spectrum of the CS ester derived from (+/-)-1-phenylethanol shows baseline resolved AB doublets for the SCH_2 moiety in the CS ester diastereomers within the range of 2.5 - 3.5 ppm (Figure 4). Assignment of these signals to the individual diastereomers has not yet been made.

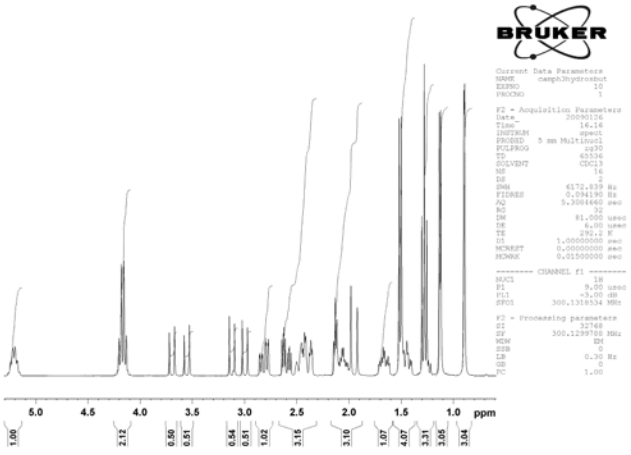

Figure 2

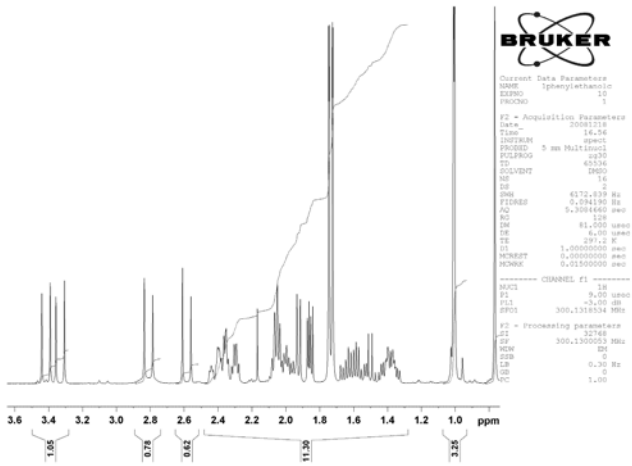

Figure 4

The ^{1}H NMR spectrum of the CS ester derived from authentic (+/-)-2-hydroxymethyloxirane shows baseline resolved signals centered at 3.1 and 3.6 ppm for the SCH_2 moiety (Figure 5). Assignment of these signals to the individual diastereomers has not yet been made.

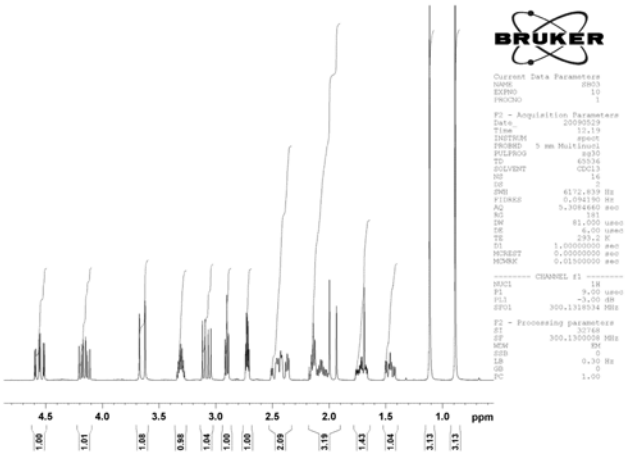

Figure 5

The ^{1}H NMR spectrum of the CS ester derived from authentic (+/-)-1-phenyl-2-propyn-1-ol shows baseline resolved signals at 5.2 and 5.6 ppm for the OCH moiety (Figure 6). Assignment of these signals to the individual diastereomers has not yet been made.

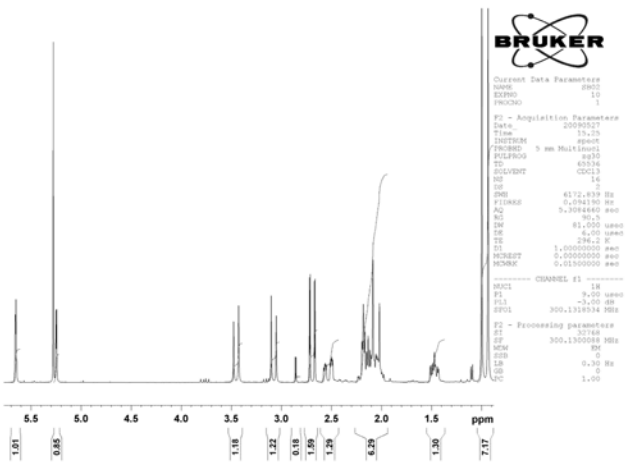

Figure 6

Conclusion

NMR spectroscopy has become a powerful method for discriminating enantiomers of chiral compounds. One such methodology is accomplished by converting the enantiomers of a chiral compound into diasteriomers using a chiral derivatizing agent. ^{1}H and ^{13}C NMR spectroscopy is then used to determine the enantiomeric ratio of the desired compound. In our experimentation, (*S*)-Camphorsulfonyl chloride proved to be a useful chiral derivetizing agent for chiral alcohols such as (+/-)-ethyl-3-hydroxybutyrate, (+/-)-2-butanol, (+/-)-1-phenylethanol, (+/-)-2-hydroxymethyloxirane, and (+/-) -1-phenyl-2-propyn-1-ol. Future work will focus on expanding the range of alcohols used for derivatization, and on assigning peaks to the camphorsulfonate esters obtained.

References

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