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Laboratory Experiment

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Using NMR Spectroscopy To Probe the Chemo- and Diastereoselectivity in the $NaBH_4$ Reduction of Benzoin Acetate and Benzoin Benzoate

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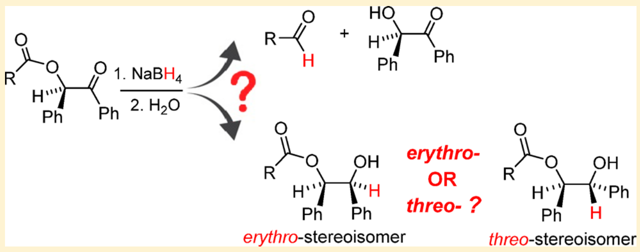
Supporting Information



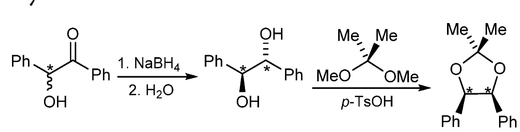
ABSTRACT: A pedagogically useful discovery-based undergraduate organic chemistry lab experiment probing the chemo- and diastereoselectivity in the $NaBH_4$ reduction of two chiral ketoesters (benzoin acetate and benzoin benzoate) has been developed. This experiment complements a previously described and highly popular discovery-based experiment that probes the stereoselectivity in the $NaBH_4$ reduction of the chiral ketone (±)-benzoin. Using reactions described in standard textbooks, students convert (±)-benzoin to the ketoester derivatives (±)-benzoin acetate and (±)-benzoin benzoate. In contrast to benzoin that has a single reducible ketone functional group, the ketoester derivatives have two reducible functional groups. In addition, the structural modifications made to the hydroxyl group of the benzoin molecule lead to an increase in the effective steric bulk of the OH group of benzoin, affording a larger acetoxy group and an even larger benzoxy group. Using NMR spectroscopy, students probe not only the chemoselectivity but also the diastereoselectivity associated with the $NaBH_4$ reduction of their difunctional substrates. In contrast to the $NaBH_4$ reduction of benzoin, which is highly diastereoselective (de ~ 100%) and affords (*R*,*S*)-hydrobenzoin with near exclusion of its (*R*,*R*)- and (*S*,*S*)- counterparts, students discover a decreasing trend in diastereoselectivity going from benzoin to benzoin acetate and benzoin benzoate. These findings are then assessed with the help of qualitative predictions made by the Felkin-Anh model for nucleophilic addition to the carbonyl group.

KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Inquiry-Based/Discovery Learning, Stereochemistry, NMR Spectroscopy, Synthesis, Aldehydes/Ketones, Diastereomers, Enantiomers, Upper-Division Undergraduate*

Pedagogically engaging discovery-based laboratory experiments[1−4] have received growing recognition by many chemical educators and there has been an increased emergence of experiments designed to "discover" specific features associated with certain chemical transformations.[5] Such experiments foster critical thinking and empower students to analyze their experimental results and logically draw specific conclusions from them.

The $NaBH_4$ reduction of the chiral ketone (±)-benzoin to a vicinal diol designed by Rowland,[6] and the determination of its stereochemistry by ^1H NMR analysis of the acetonide derivative of the diol, is a remarkably successful and illustrative example of a discovery-based experiment. The sequential reduction of racemic benzoin to a vicinal diol with two stereogenic centers, followed by conversion of the diol to an acetonide (Scheme 1), and observation of two well-resolved singlets of equal intensity for the geminal methyl groups in the ^1H NMR spectrum of the acetonide, enables a student to draw the logical conclusion that the $NaBH_4$ reduction of (±)-benzoin is highly diastereoselective (de ~100%) and that (*R*,*S*)-hydrobenzoin (a.k.a., *meso*-hydrobenzoin) is produced with near exclusion of its diastereomeric counterparts (*R*,*R*)- and (*S*,*S*)-hydrobenzoins.

Scheme 1. Distereoselective Reduction of (±)-Benzoin to (*R*,*S*)-Hydrobenzoin and Formation of Acetonide Derivative



The selective formation of (*R*,*S*)-hydrobenzoin in this reaction also sets the stage for further discussion on the influence of a stereogenic center in proximity of a prochiral carbonyl group, which in turn leads to consideration of stereochemical models that have been postulated for predicting the preferred diastereoselection in nucleophilic additions to carbonyl compounds (the Cram and Felkin-Anh models).[7] The Felkin-Anh model takes into account the differences in effective steric bulks of the three ligands attached to the stereogenic α-carbon (Ph, OH, and H), places the largest group (L = Ph) orthogonal to the carbonyl group, and predicts the least hindered trajectory of nucleophilic attack as that where the hydride ion approaches alongside the small group (S = H) at

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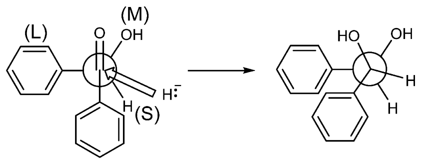
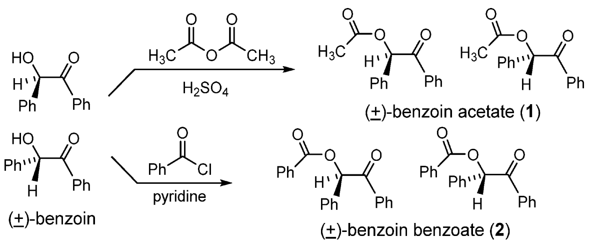
the Bürgi-Dunitz angle[8] of about 107° leading to (*R*,*S*)-hydrobenzoin (Scheme 2).

Scheme 2. Least Hindered Trajectory for Attack of Hydride Ion As Predicted by the Felkin-Anh Model Leading to (*R*,*S*)-Hydrobenzoin (L = Large; M = Medium; S = Small)



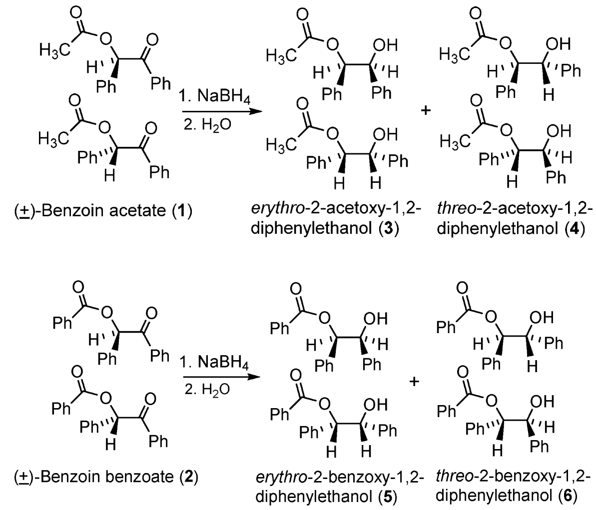
On the basis of the Felkin-Anh model, it is expected that if the effective steric bulks of any two ligands on the *α*-stereogenic center were to become more similar, the diastereoselectivity of the reaction would become less pronounced (i.e., de <100%) and the reaction should lead to a *mixture* of diastereomers rather than a *single* diastereomer. As a sequel to Rowland's classic experiment, an undergraduate experiment has been developed that explores the $NaBH_4$ reduction of two substrates derived from benzoin (Scheme 3): benzoin acetate (**1**) and benzoin benzoate (**2**). In contrast

Scheme 3. Synthesis of (±)-Benzoin Acetate (1) and (±)-Benzoin Benzoate (2)



to benzoin that has a single reducible ketone functional group, compounds **1** and **2** are ketoesters having two different reducible functional groups. Furthermore, in ketoesters **1** and **2**, the OH group of benzoin is modified to a larger acetoxy group (CH_3CO_2) and even larger benzoxy group ($PhCO_2$), respectively. Thus, using substrates **1** and **2**, students can explore not only any chemoselectivity exhibited by the $NaBH_4$ reduction of these difunctional compounds, but also any decrease in the diastereoselection in light of the prediction made by the Felkin-Anh model. Using reactions described in standard textbooks, students synthesize and isolate ketoesters **1** and **2** and then proceed to reduce them with sodium borohydride (Scheme 4). Using ^{1}H NMR spectroscopy, students "discover" that $NaBH_4$ reductions of their substrates are highly chemoselective and that the ketone function is selectively reduced while the ester function remains intact. Also, based on their NMR data, they "discover" that reduction of compounds **1** and **2** affords *mixtures* of the *erythro*- and *threo*-diastereomers **3**/**5** and **4**/**6**, respectively.[9] These findings lead to a postclassroom discussion on the chemo- and diastereoselectivity of $NaBH_4$ reductions of the chiral ketoesters **1** and **2** as revealed by ^{1}H NMR data and the general application of the Felkin-Anh model for nucleophilic addition to the carbonyl group. Therefore, students' objectives are (1) synthesize compounds **1** and **2** by acylating (±)-benzoin using two common acylating reagents (acetic anhydride and benzoyl chloride), (2) carry out sodium borohydride reductions of

Scheme 4. $NaBH_4$ Reduction of (±)-Benzoin Acetate (1) and (±)-Benzoin Benzoate (2)



ketoesters **1** and **2**, (3) analyze the ^{1}H NMR spectra of ketoesters **1** and **2** along with their reduced products and draw conclusions regarding the chemo- and diastereoselectivity of the reductions, and (4) assess the diastereoselectivity of their reductions in light of the Felkin-Anh model for nucleophilic addition to the carbonyl group.

■ EXPERIMENT

This experiment was performed over two consecutive laboratory periods by 127 students enrolled in 7 lab sections of a second-semester introductory organic laboratory course. Students work individually. During the first week, students convert (±)-benzoin to (±)-benzoin acetate (**1**)[10] and (±)-benzoin benzoate (**2**)[11] by adaptation of known procedures (Scheme 3): (±)-benzoin (0.010 mol) and acetic anhydride (0.021 mol in glacial acetic acid) or benzoyl chloride (0.017 mol in pyridine) are refluxed, after which the crude products **1** and **2** are collected following an aqueous workup. In the second week, ketoesters **1** and **2** are reduced with $NaBH_4$ following the same protocol as that used for the reduction of (±)-benzoin (Scheme 4): **1** or **2** (0.0028 mol in 95% ethanol) and powdered $NaBH_4$ (0.0032 mol) are swirled for 30 min, after which the crude reduced products **3**/**4** or **5**/**6** are collected following an aqueous workup.[6] ^{1}H NMR spectra are recorded in $CDCl_3$ (TMS internal standard). For comparative purposes, ^{1}H NMR spectra of (±)-benzoin and authentic samples of hydroxyesters **3** and **5**[9] are provided. In a postlaboratory session, NMR spectra for all compounds are analyzed for the chemo- and diastereoselectivity associated with the $NaBH_4$ reduction of ketoesters **1** and **2**. Detailed procedures for the preparation of ketoesters **1** and **2**, their reduced products **3**/**4** and **5**/**6**, and full NMR spectral data are in the Supporting Information.

■ HAZARDS

Laboratory coats, safety goggles, and disposable Nitrile gloves must be worn during the experiment. Benzoin, glacial acetic acid, acetic anhydride, ethanol, pyridine, and benzoyl chloride are all flammable, skin, eye, and respiratory irritants. Glacial acetic acid, acetic anhydride, benzoyl chloride, and concentrated sulfuric acid are corrosive and can cause severe skin burns and eye damage. Chloroform-*d* causes skin and severe

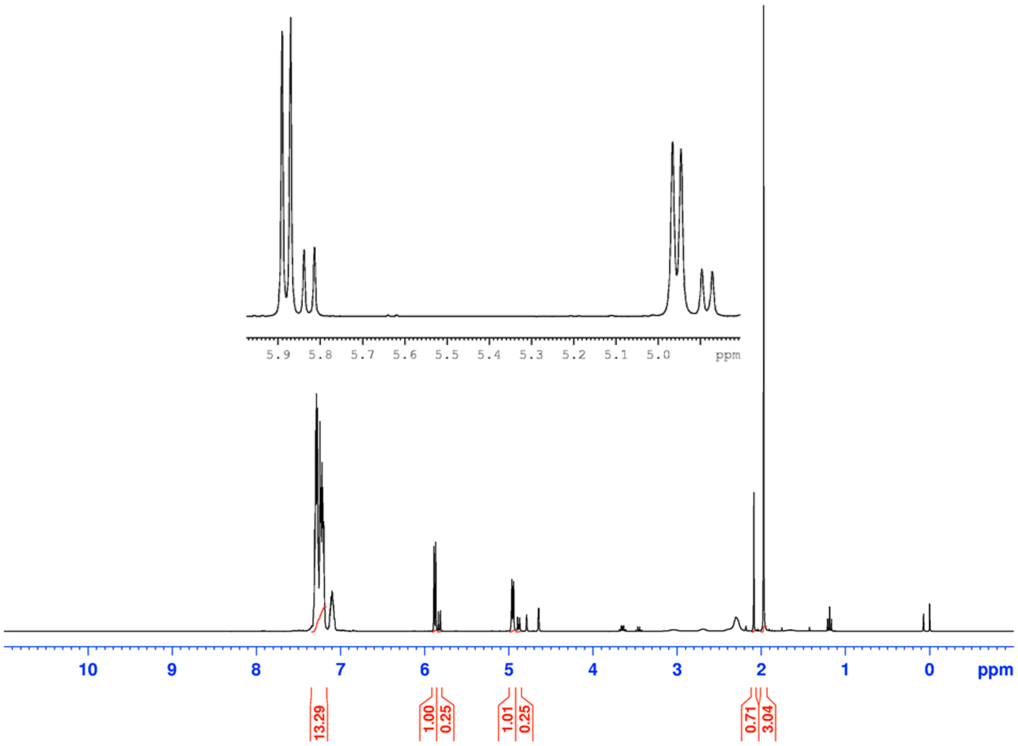


Figure 1. [1]H NMR spectrum (300 MHz) of *crude product* from $NaBH_4$ reduction of benzoin acetate (**1**).

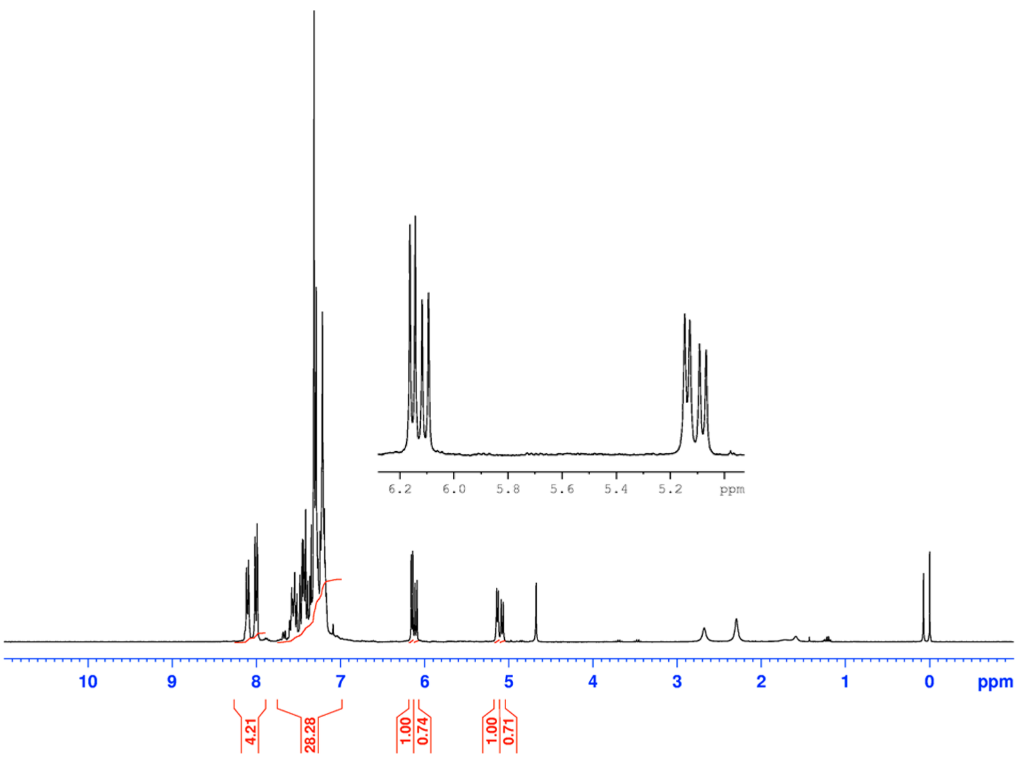


Figure 2. [1]H NMR spectrum (300 MHz) of *crude product* from $NaBH_4$ reduction of benzoin benzoate (**2**).

eye irritation and is a suspected carcinogen; avoid contact with skin and eyes and inhalation of vapors. Handle all liquid reagents in well-ventilated fume hoods. Sodium hydroxide is corrosive and causes severe eye damage. Sodium borohydride reacts with acids and protic solvents to liberate flammable hydrogen gas. The hazards associated with the products are unknown; they are all flammable and care must be taken to avoid contact with skin and eyes.

DISCUSSION

The crude product typically obtained by students from the $NaBH_4$ reduction of (±)-benzoin acetate (**1**) displayed distinct [1]H NMR spectral patterns for diastereomers **3** and **4** as the

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main products: two pairs of well-resolved doublets with unequal peak areas at 5.88 and 4.96 ppm (J = 6.0 Hz), as well as at 5.82 and 4.88 ppm (J = 7.4 Hz) for the vicinal methine hydrogens of **3** and **4**, respectively (Figure 1). These *distinct* resonances clearly indicated that the product was, indeed, a *mixture* of the two diastereomers and that the ketone function was selectively reduced while the ester function remained intact. The NMR spectrum of the crude product also displayed two singlets at 1.97 and 2.09 ppm that were attributable to the acetoxy CH_3 groups of **3** and **4**, respectively, further indicating that the ester function had not been reduced by $NaBH_4$ and that the product was a mixture of diastereomers **3** and **4**. The assignment of the doublets at 5.88 and 4.96 ppm and the singlet at 1.97 ppm to diastereomer **3** came from a perfect match of these peaks with the corresponding peaks from an authentic sample of **3**.[9] NMR integration of the doublets revealed a ratio of 80:20 for diastereomers **3** and **4**, respectively. Nearly the same diastereomeric ratio (81:19) was obtained from integration of the singlets. These ratios reflected a greater steric effect exerted by the larger acetoxy group in **1** (in comparison to the OH group in benzoin) leading to a *decrease* in the diastereomeric excess from near 100% to 60%, and was in accord with the qualitative prediction by the Felkin-Anh model. The ^{1}H NMR spectrum of a typical student product obtained from the reduction of (±)-benzoin benzoate (**2**) also displayed two pairs of doublets of unequal intensities for the vicinal methine hydrogens in *erythro*-2-benzoxy-1,2-diphenylethanol (**5**) and *threo*-2-benzoxy-1,2-diphenylethanol (**6**) (Figure 2). NMR integration of these doublets revealed a ratio of 58:42 (de ~16%) for diastereomers **5** and **6**, respectively. Evidently, the increased steric effect of the benzoxy group (approaching that of a phenyl group) led to a more balanced mixture of diastereomers **5** and **6**. This finding was in complete agreement with that qualitatively predicted by the Felkin-Anh model. The observed decreasing trend in diastereoselectivity for the $NaBH_4$ reductions of benzoin (de ~100%) and the ketoesters **1** and **2** (de ~60% and 16%, respectively) followed progressive increases in steric bulks of the α-carbon groups going from hydroxy, to acetoxy, and benzoxy, respectively.

Integration of the aromatic signals for diastereomers **5** and **6** pointed to the presence of three phenyl groups, a further indication that the ester function of **2** remained intact. Of note was that certain student samples of diastereomers **3**/**4** and **5**/**6** showed NMR spectra in which the upfield methine doublets were further split into doublet of doublets as a result of additional C−H/O−H coupling and, as expected, the O−H signals appeared as doublets as well (Figure 5S and Figure 9S, Supporting Information).

■ CONCLUSION

Probing the ^{1}H NMR spectra of the products obtained from the $NaBH_4$ reduction of benzoin acetate (**1**) and benzoin benzoate (**2**) clearly showed that progressively increasing the steric size of the α-carbon group in benzoin from OH to a somewhat larger acetoxy group, and an even larger benzoxy group, decreased the diastereoselectivity of the reduction (de ~100% for benzoin) and afforded increasingly more apportioned mixtures of diastereomers **3**/**4** (de ~60% for **1**) and **5**/**6** (de ~16% for **2**). These findings were in complete agreement with the qualitative diastereoselectivity predictions by the Felkin-Anh model. Furthermore, the appearance of singlets for the methyl groups in the ^{1}H NMR spectra of diastereomers **3**/**4** along with doublets for the methine hydrogens of **3**/**4** and **5**/**6** confirmed that $NaBH_4$ chemoselectively reduced the ketone carbonyl, while the ester carbonyl was left intact.

■ ASSOCIATED CONTENT

Supporting Information

Student handouts; notes for the instructors; list of hazards; experimental procedures for the preparation of ketoesters **1** and **2** and their sodium borohydride reductions; author-obtained ^{1}H NMR spectra of associated compounds. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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