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NMR Separation of β-Prochiral Protons to the Ether Oxygen of Chiral Esters with Lanthanide Shift Reagents

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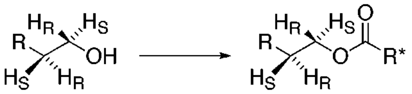
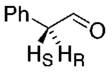
ABSTRACT



The use of chiral ester derivatives of 2-phenylethan-1-ol in conjunction with chiral lanthanide shift reagents allows separation of the prochiral and homo prochiral protons to the ether oxygen in the NMR spectrum. Specifically the α- and β- protons of the *N*-(4-nitrophenylsulfonyl)-L-phenylalanyl ester of 2-phenylethan-1-ol, after addition of either europium *d*- *or l*-3-heptafluorobutyrylcamphorate or ytterbium *d*-3-heptafluorobutyrylcamphorate are differentiated. This is the first report of the NMR separation of prochiral protons β to an ester linkage.

During the course of our investigations on acid-catalyzed rearrangement of unsymmetrical optically active deuterated epoxides to aldehydes, we required a method to distinguish the prochiral protons (deuteron) β to the oxygen functionality, which are chiral by virtue of isotopic substitution, in the product aldehyde **1** or of the corresponding alcohol **2**. The study is directed to measure prochiral proton selection for migration of hydride from C1 to C2.[1] The extent of retention and inversion in the rearrangement requires a measure of the relative population of hydrogen and deuterium at each of the prochiral β-positions.



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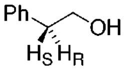

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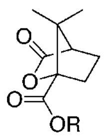
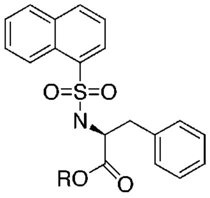
Methods already exist for distinguishing the prochiral protons α to the alcohol **2**.[2] Conversion of the alcohol to a chiral ester, for example, optically active camphanyl ester **3a**, results in the α- and β-protons becoming magnetically nonequivalent.[3] To date, NMR resolution of prochiral β-protons to oxygen has not been reported.

We now report a study of four chiral esters **3a**, **4a**, **5a**, and **6a** of 2-phenylethan-1-ol prepared by reaction with (1*S*)-(−)-camphanic chloride, *N*-(1-naphthalenesulfonyl)-*S*-phenylalanyl chloride, *N*-(*p*-toluenesulfonyl)-*S*-phenylalanyl chloride and *N*-(4-nitrophenylsulfonyl)-*S*-phenylalanyl chloride. For each of these four esters the β-prochiral hydrogens were not distinguishable in the NMR spectra, and although the α-prochiral protons showed some nonequivalence, incomplete resolution made population analysis difficult.



3a: R= $Ph(CH_2)_2$
3b: R= $CH_3(CH_2)_7$



4a: R= $Ph(CH_2)_2$
4b: R= $CH_3(CH_2)_7$

In an attempt to enhance the magnetic asymmetry of the β-hydrogens we investigated the NMR spectrum (300 MHz) of the diastereomeric complexes formed by addition of

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[1] Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **2000**, 65, 8421−8429.

[2] (a) Schwab, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 1876−1878. (b) Shapiro, S.; Arunachalam, T.; Caspi, E. *J. Am. Chem. Soc.* **1983**, *105*, 1642−1646.

[3] (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457. (b) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274−275.

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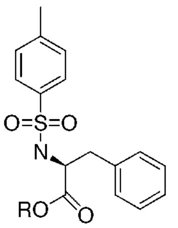
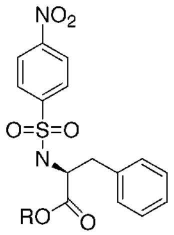


5a: R= Ph$(CH_2)_2$
5b: R= $CH_3(CH_2)_7$



6a: R= Ph$(CH_2)_2$
6b: R= $CH_3(CH_2)_7$
6c: R= Me-Ph$(CH_2)_2$

optically active ytterbium *d*-3-heptafluorobutyrylcamphorate (*d*-Yb$(hfc)_3$) and the *l*- and *d*-forms of europium heptafluorobutyrylcamphorate (Eu$(hfc)_3$).

Addition of *l*- or *d*-Eu$(hfc)_3$ shift reagents to the esters of 2-phenylethanol **3a**, **4a**, and **5a** resulted in differentiation of the α-prochiral protons with sufficient clarity to allow accurate NMR integration. However, no separation of the *β*-prochiral protons was observed. The shift of the prochiral α- (and *β*-) protons is the same whether *l*- or *d*-Eu$(hfc)_3$ is used, showing the asymmetry of the ligand for the diastereomeric complexes was not transmitted to these protons. Similarly the downfield shifts of protons H1−H8 on addition of *d*-Yb$(hfc)_3$ shift reagent to **3a**, **4a**, and **5a** show that H3 and H4, α to the ester linkage, are differentiated but the *β*-protons are not (Figure 1).[4]

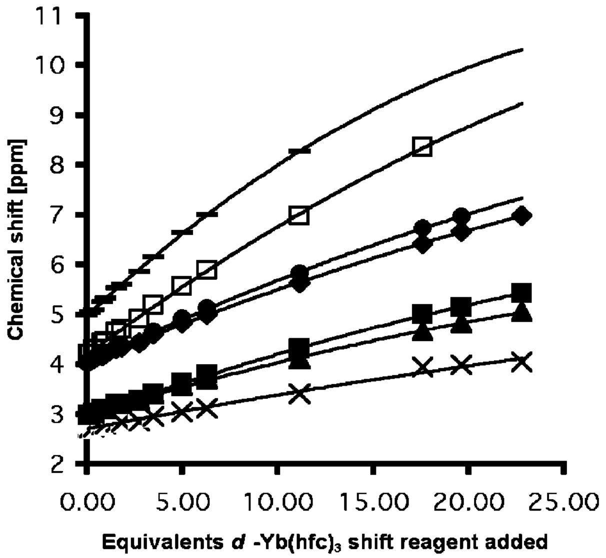


Figure 1. Graph showing the downfield shift of the proton resonances of **5a** with added shift reagent. H1 ×, H2 ×, H3 ◆, H4 ●, H5 ▲, H6 ■, H7 □, H8 −. (Symbol × is used for both H1 and H2 in this particular graph as they are not differentiated).

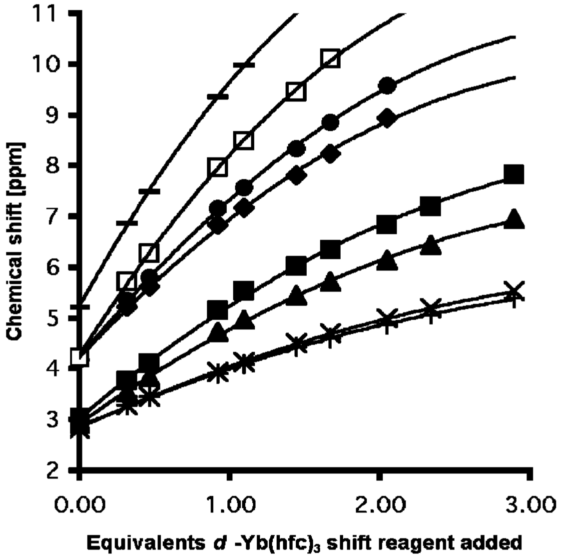
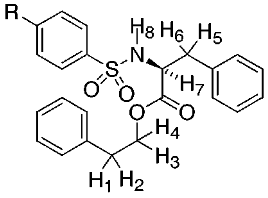


Figure 2. Graph showing the downfield shift of the proton resonances of **6a** with added shift reagent. H1 +, H2 ×, H3 ◆, H4 ●, H5 ▲, H6 ■, H7 □, H8 −.

Complexation of the nitro ester **6a** with *d*-Yb$(hfc)_3$, (Figure 2)[5] or *d*- or *l*-(Eu$(hfc)_3$) in all cases resulted in NMR differentiation of the α- (H3 and H4) and *β*- (H1 and H2) prochiral protons.



5a: R= CH_3
6a: R= NO_2

At the concentration of *d*- and *l*-Eu$(hfc)_3$ necessary to separate the *β*-prochiral protons, a broad signal of the shift reagent appeared with the *β*-protons and made integration inaccurate. This does not occur with *d*-Yb$(hfc)_3$, and so even though the proton signals are somewhat broader than with the europium shift reagent, integration of the *β*-protons is more accurate.

For the corresponding esters of 1-octanol **3b**−**6b** no differentiation of the *β*-prochiral protons was achieved on addition of *d*-Yb$(hfc)_3$) and *d*-Eu$(hfc)_3$, although in all cases the α-prochiral protons were differentiated.

In a further example, resolution of the α- and *β*-prochiral protons occurred for the corresponding ester of 2-*p*-methylphenylethanol **6c** on addition of *d*-Yb$(hfc)_3$, indicating that an aromatic substituent *β* to the ether oxygen is a necessary structural feature for differentiation of the *β*-prochiral

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[4] The results for **3a** with *d*-Yb$(hfc)_3$ and **4a** with *d*-Eu$(hfc)_3$ are similar to those for **5a**.

[5] The smaller downfield shift of all proton signals per equivalent of shift reagent for **5a** compared to **6a** could reflect differences in equilibrium constant for the formation of the ester−shift reagent complexes.

protons. This aryl substituent may be involved in intramolecular π-stacking and impose the necessary asymmetry to the β-proton environment for differentiation.

The observation that it is possible to separate the prochiral C2 protons in the NMR spectrum of ester derivatives of 2-phenylethanol makes possible analysis of the stereoselective deuteration of alcohols and hydride migration using selectively deuterated starting materials.

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Supporting Information Available: ^{1}H NMR and a detailed description of experimental procedures for compounds **3a**−**6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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