

## Enantiomeric purity of alkylmethylphenylsulfonium ions with chiral NMR shift reagents: racemization by pyramidal inversion as observed by $^1\text{H}$ NMR spectroscopy

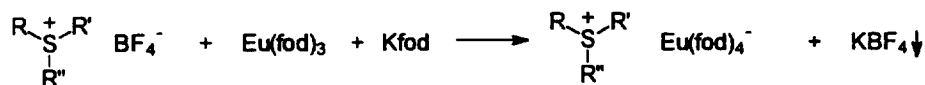
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**Abstract:** Chiral tetrakis europate anions are used to spectroscopically resolve racemic mixtures of chiral alkylmethylphenylsulfonium ions using  $^1\text{H}$  NMR spectroscopy. The alkyl groups include ethyl, *n*-butyl, *n*-octyl and benzyl. The shift reagents include both  $\text{Eu}(\text{tfc})_3\text{fod}^-$  and  $\text{Eu}(\text{tfc})_4^-$ , where *tfc* is chiral (+)-3-(trifluoromethylhydroxymethylene)camphorate and *fod* is 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione. Assignment of R and S configuration in the NMR spectrum of ethylmethylphenylsulfonium ion was made by synthesis of the R-enriched mixture of ethylmethyl-*p*-tolylsulfonium ion. Racemization of this mixture was observed by  $^1\text{H}$  NMR spectroscopy by heating to 60°C. © 1997 Elsevier Science Ltd

We wish to report on the use of a chiral NMR shift reagent for the assessment of enantiomeric purity of a series of alkylmethylphenyl sulfonium ions using  $^1\text{H}$  NMR spectroscopy. The alkyl groups include ethyl (I), *n*-butyl (II), *n*-octyl (III) and benzyl (IV). The shift reagents include both  $\text{Eu}(\text{tfc})_3\text{fod}^-$  and  $\text{Eu}(\text{tfc})_4^-$ , where *tfc* is (+)-3-(trifluoromethylhydroxymethylene)camphorate and *fod* is 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione. Assignment of R and S configuration in the NMR spectrum of I was made by synthesis of the R-enriched mixture of I. Racemization of this mixture was observed by  $^1\text{H}$  NMR spectroscopy by heating to 60°C.

In 1987 Wenzel and Zaia reported the use of NMR lanthanide shift reagents for the analysis of sulfonium and isothiuronium salts.<sup>1</sup> They found that when the europate complex,  $\text{Eu}(\text{fod})_3$ , is reacted with  $\text{Kfod}$  in the presence of a sulfonium tetrafluoroborate, ion pair formation occurs between the sulfonium cation and the tetrakis europate anion,  $\text{Eu}(\text{fod})_4^-$ . Precipitation of potassium fluoroborate drives the reaction toward ion-pair formation (Scheme 1).



Scheme 1.

The use of  $\text{Agfod}$  is recommended when sulfonium halides are analyzed since precipitation of silver halide forces ion-pair formation.

The sulfonium tetrafluoroborates salts were prepared as racemic mixtures by established procedures.<sup>2</sup> The procedure of Wenzel and Zaia was used for preparation of 0.1M sulfonium cation–shift reagent ion pairs in *d*-chloroform using  $\text{Eu}(\text{tfc})_3$  with either  $\text{Kfod}$  or  $\text{Ktfc}$ .<sup>1</sup> The mixtures were stirred for 30 min before centrifuging and removing the precipitated  $\text{KBF}_4$ .

Figure 1 shows the unshifted spectrum of I in *d*<sub>6</sub>-acetone. The ortho hydrogen resonances are expanded since they are the focus of this study. Figure 2 shows the shifted spectrum of I using the chiral shift reagent  $\text{Eu}(\text{tfc})_3\text{fod}^-$ . The methylene hydrogens are strongly shifted and appear as two

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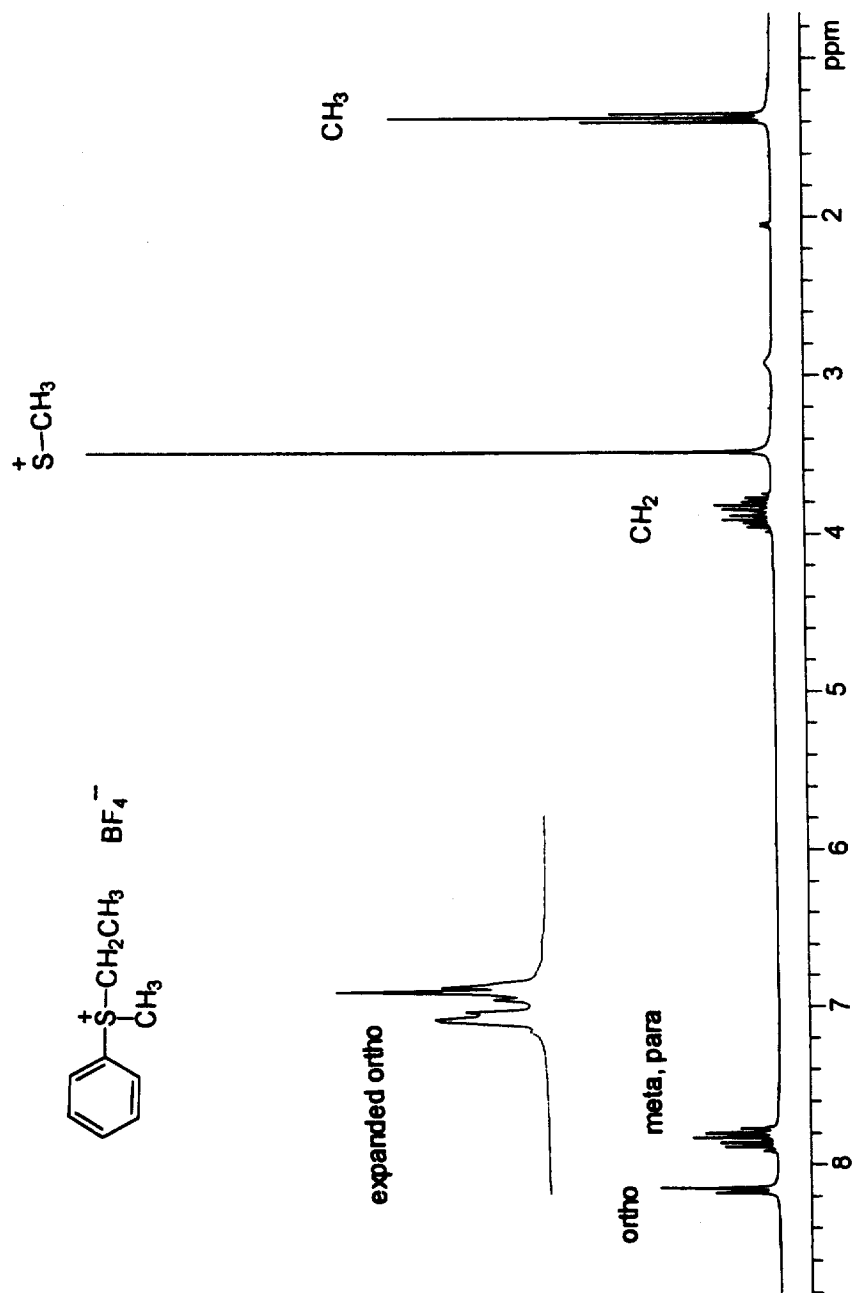


Figure 1.  $^1\text{H}$  NMR spectrum of ethylmethylphenylsulfonium tetrafluoroborate in  $d_6$ -acetone.

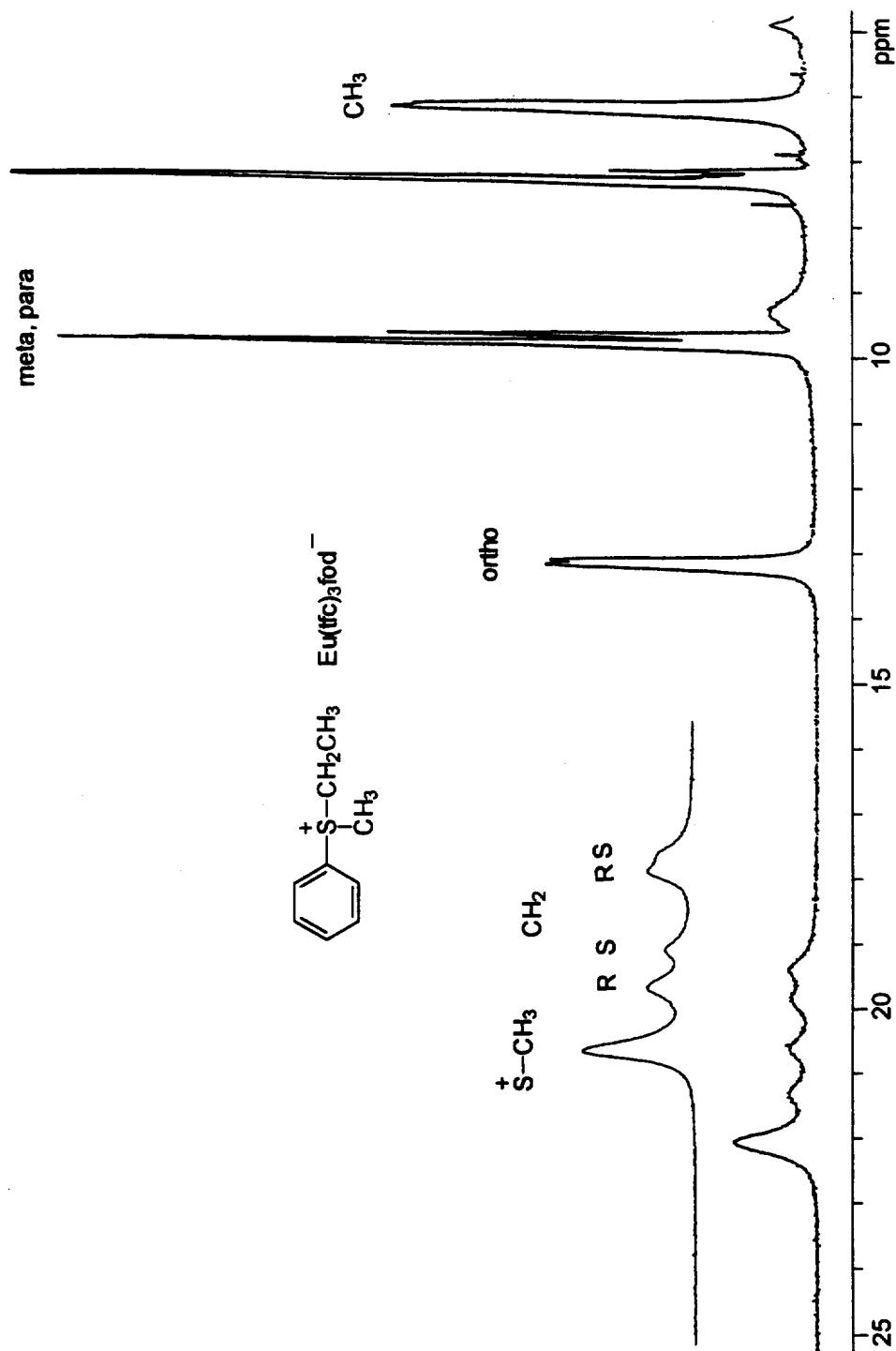


Figure 2. Partial  $^1\text{H}$  NMR spectrum of ethylmethylphenylsulfonium cation in the presence of chiral shift reagent  $\text{Eu}(\text{fod})_3\text{fod}^-$ .  
Solvent:  $\text{CDCl}_3$ , 0.10 M,  $20^\circ\text{C}$ .

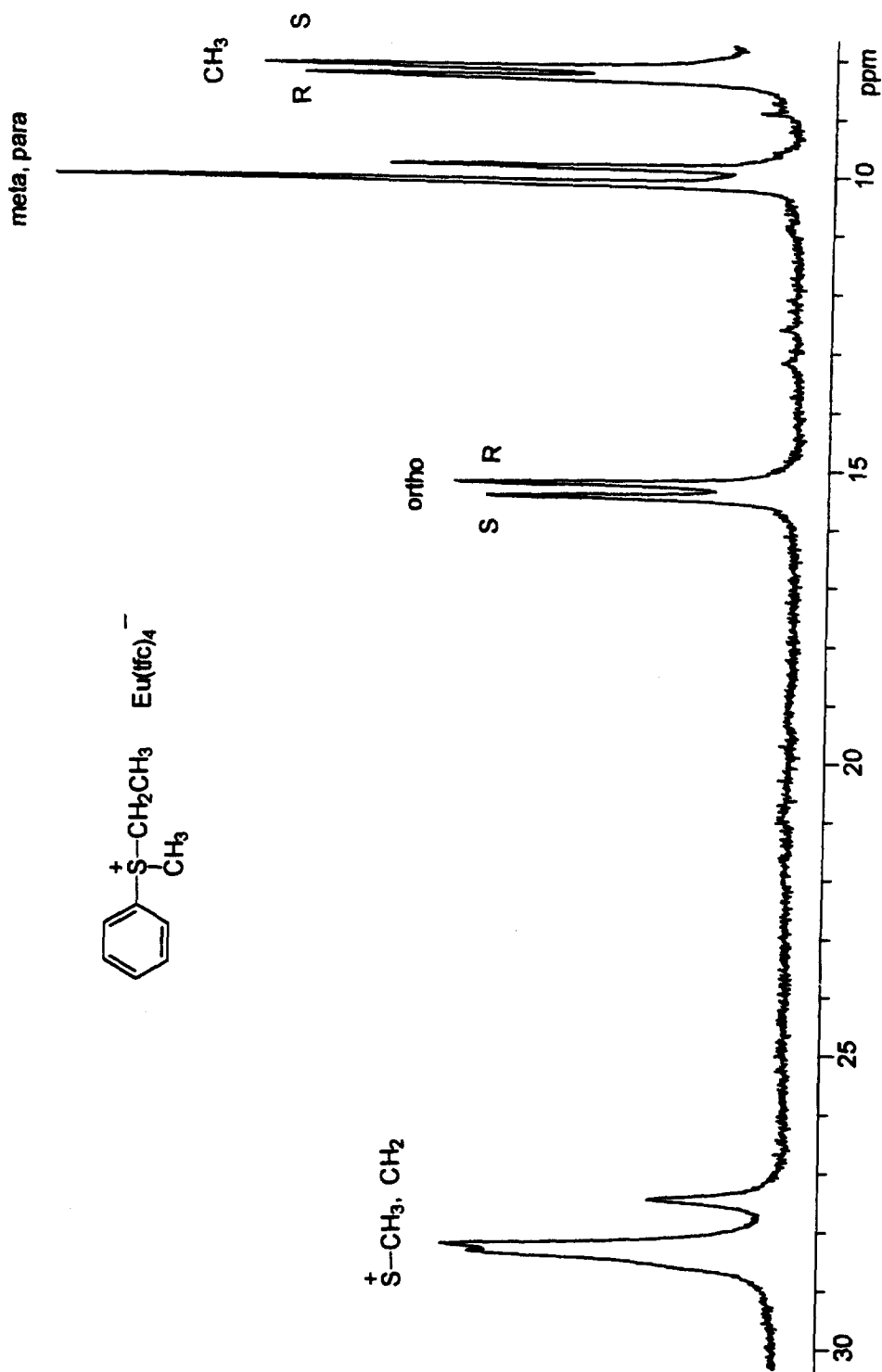
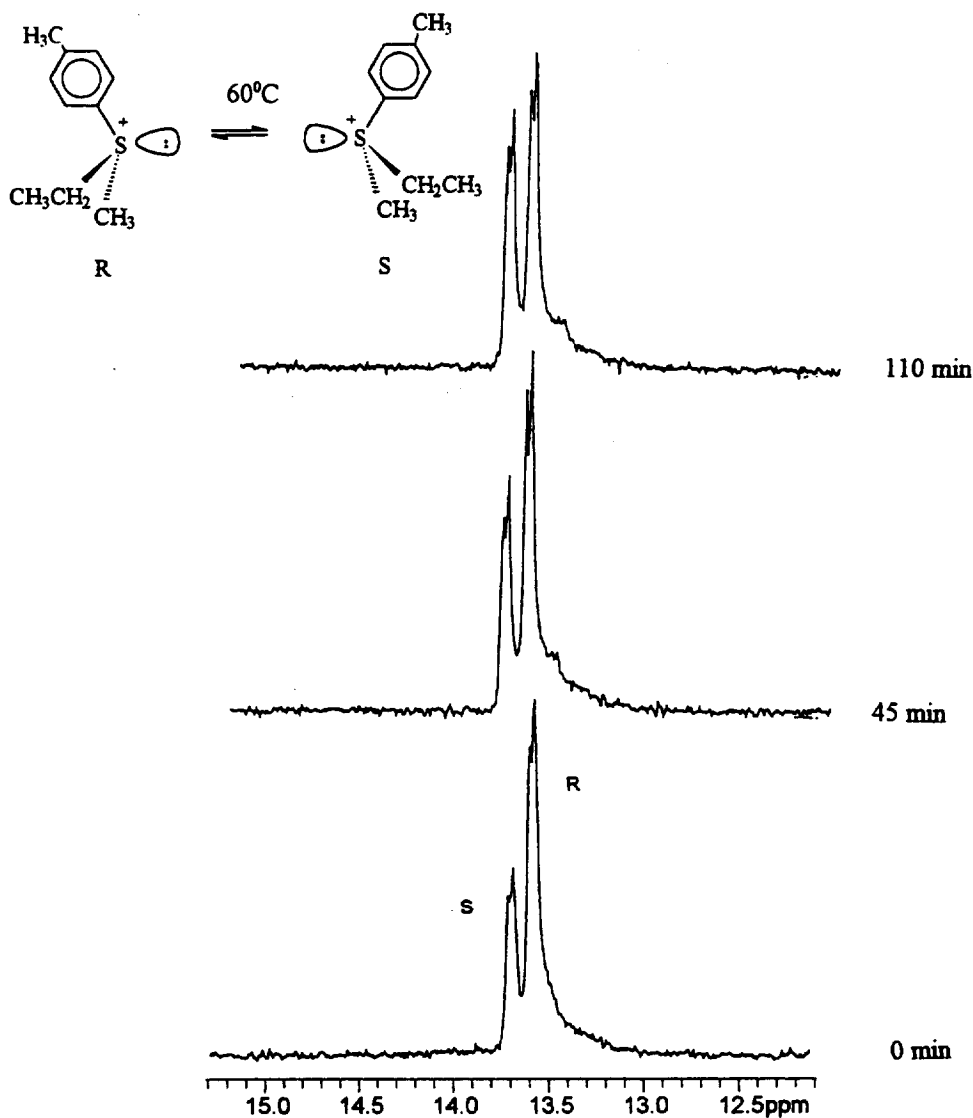


Figure 3. Partial  $^1\text{H}$  NMR spectrum of ethylmethylphenylsulfonium cation in the presence of chiral shift reagent  $\text{Eu}(\text{tfc})_4^-$ .  
Solvent:  $\text{CDCl}_3$ ,  $0.10\text{ M}$ ,  $20^\circ\text{C}$ .



**Figure 4.** Partial  $^1\text{H}$  NMR spectrum of R-enriched ethylmethyl-*p*-tolylsulfonium ion in the presence of chiral shift reagent  $\text{Eu}(\text{tfc})_4^-$  at  $60^\circ\text{C}$ . Ortho hydrogen resonances are shown.

broad doublets in the region of 19–21 ppm. The methyl signal at 22 ppm appears as one broad singlet with no enantiomeric resolution. The ortho hydrogen resonances are slightly resolved with a doublet at 13.2 ppm. The spacing of this doublet is 19.5 Hz, considerably greater than 7.3 Hz observed for the ortho–meta coupling of the unshifted sulfonium ion.

Assignment of R and S configuration for the methylene hydrogens was made by first synthesizing (R)-ethylmethyl-*p*-tolylsulfonium tetrafluoroborate from (R)-methyl-*p*-tolylsulfoxide using trimethylloxonium tetrafluoroborate followed by addition of diethylcadmium.<sup>3</sup> This synthesis has been shown to take place with excess inversion of configuration,<sup>4</sup> resulting in a mixture that is enriched in the R isomer. The shifted spectrum of this enriched product is shown above that of the racemic mixture in Figure 2. The methylene hydrogens of the R isomer are more intense, allowing us to make assignments.

The shifted spectrum using the chiral shift reagent  $\text{Eu}(\text{tfc})_4^-$  is shown in Figure 3. The methylene

meta, para

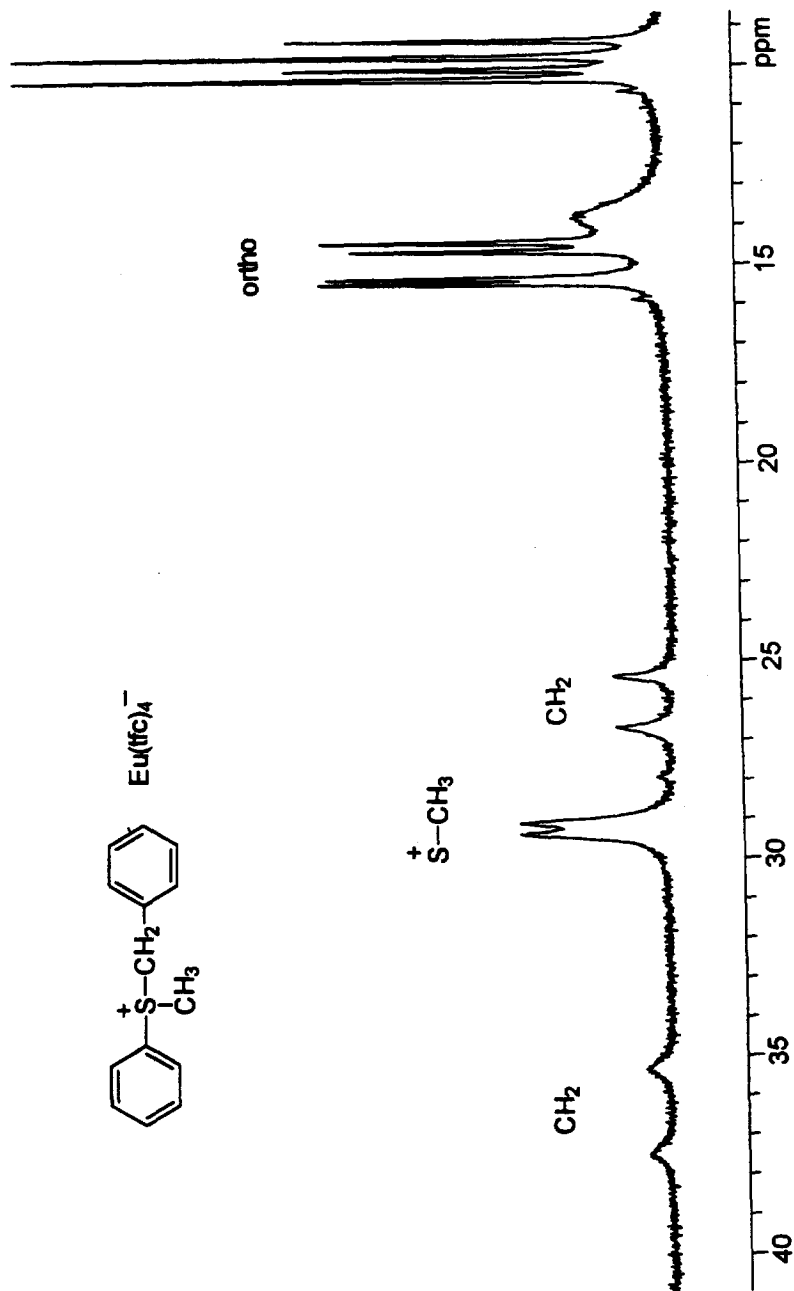


Figure 5. Partial  $^1\text{H}$  NMR spectrum of benzylethylmethylsulfonium cation in the presence of chiral shift reagent  $\text{Eu}(\text{tfc})_4^-$ .  
Solvent:  $\text{CDCl}_3$ , 0.10 M, 20°C.

and methyl hydrogen resonances overlap with each other near 28 ppm, with no apparent enantiomeric resolution. However, the ortho hydrogen resonances (15 ppm) are enantiomerically resolved with peak maxima separated by 73.2 Hz (0.27 ppm) and the methyl resonances of the ethyl group are also resolved. Spin-spin splitting is lost in this spectrum due to line broadening caused by the shift reagent. Assignments were made as described above. Deconvolution of the ortho hydrogen and methyl resonances reveal an enantiomeric excess of 22%.

It is well known that dialkylarylsulfonium ions racemize by pyramidal inversion at significant rates above room temperature.<sup>5-8</sup> To observe this process, the ethylmethyl-*p*-tolylsulfonium-Eu(tfc)<sub>4</sub><sup>-</sup> ion pair in *d*-chloroform was heated in a sealed tube to 60°C and spectra were obtained as function of time. This result is shown in Figure 4 where the signals of the ortho hydrogens are shown. The signal of the S isomer increases with time relative to the R isomer, which indicates racemization of the R and S isomers.

Racemic mixtures of sulfonium ions II-IV were also examined. For II and III, best resolution was observed for the ortho hydrogen resonances using Eu(tfc)<sub>4</sub><sup>-</sup> as shift reagent. Absolute assignments were not made. We found the methylene resonances of IV to be highly resolved with Eu(tfc)<sub>4</sub><sup>-</sup>. The spectrum, shown in Figure 5, shows both diastereotopic methylene hydrogen resonances to be enantiomerically resolved at 36.5 and 26 ppm. In addition, the methyl and ortho hydrogen resonances are enantiomerically resolved, with best resolution obtained on the ortho hydrogen resonances of the more upfield benzyl group. Enantiomeric assignments of R and S could not be made.

It is clear from these results that chiral tetrakis europate anions may be useful for measuring enantiomeric excess of some alkylmethylphenyl sulfonium ions, providing absolute assignments can be made. This rapid, convenient NMR method requires at most about 30 mg of material and, in contrast to chiroptical methods,<sup>6,7</sup> does not require comparison with an enantiomerically-pure sample for measurement of enantiomeric excess. The enantiomeric resonances are not always baseline resolved but this does not necessarily detract from the method, since deconvolution of the curves should be a simple matter. Pyramidal inversion of a sulfonium ion was observed for the first time by NMR spectroscopy in the presence of an NMR shift reagent.

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