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# Chemical synthesis of [<sup>2</sup>H]-ethyl tosylate and exploration of its crypto-optically active character combining complementary spectroscopic tools

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## ABSTRACT:

Small chiral molecules are excellent candidates to push the boundaries of enantiodiscrimination analytical techniques. Here is reported the synthesis of two new deuterated chiral probes, (*R*)- and (*S*)-[<sup>2</sup>H]-ethyl tosylate obtained with high *ee*'s. Due to their crypto-optically active properties, the discrimination of each enantiomer is challenging. While their enantiopurity is determined by <sup>2</sup>H-NMR in chiral anisotropic media, their identification was performed by combining quantum chemical calculations and vibrational circular dichroism analysis.

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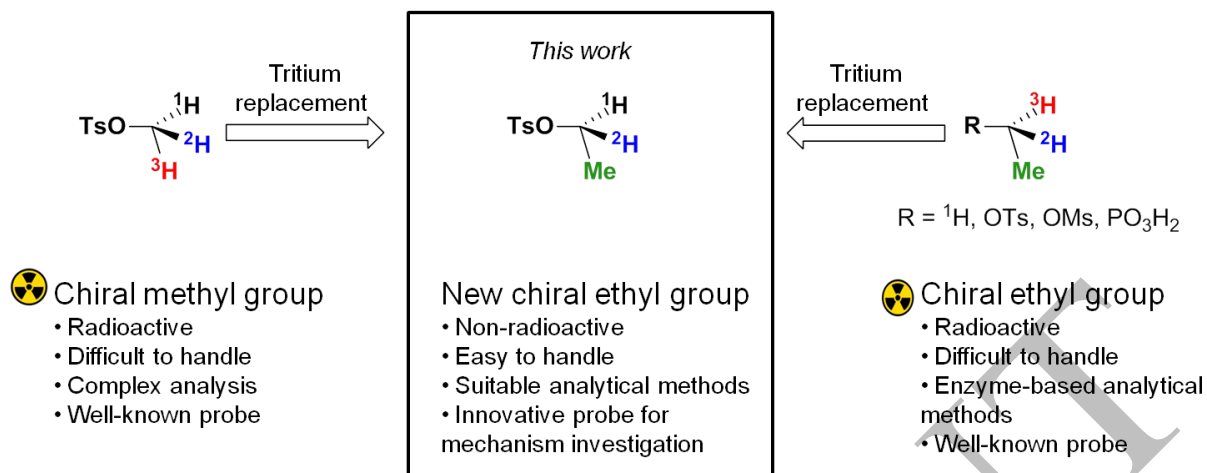
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Chirality is a key molecular property that confers specific characteristics to matter. Due to the single spatial orientation of chiral compounds, numerous applications are found in Biology, Chemistry, Physics but also in Materials Science.<sup>1</sup> Enantiodiscrimination based on planar light polarization is a routine tool to distinguish optically active isomers. However, this approach fails for analyzing crypto-optically active compounds<sup>2</sup> which are ideal candidates to explore the limits of detection and identification of modern analytical techniques.

From an application viewpoint, crypto-optically active entities show a strong potential as probes for enzymatic or chemical mechanisms studies.<sup>3</sup> The smallest of them, the chiral methyl group  $-C^1H^2H^3H$ , has been widely described and used to advance knowledge of living processes. Notably, it has been very helpful for the understanding of methyl transferase enzymes mechanism.<sup>4</sup> Nevertheless, the use of the chiral methyl group suffers from the following drawbacks: i) the presence of a radioactive tritium atom causing difficulties in terms of synthesis, handling, storage, analysis and waste management; ii) the challenging measurement of *ee* in the case of isotopic chirality. So far, only fastidious synthesis of a well-controlled diastereoisomer (without epimerization of the chiral centre) or enzymatic resolution, both associated with  $^3H$  NMR analysis have been disclosed to determine *ee*'s.<sup>4a,5</sup> To circumvent these limitations, the design of specific deuterium-labelled probes may simplify the generation of stereogenic centres thanks to the non-radioactive nature of these analytes and their analysis with the possibility to use advanced techniques such as  $^2H$  NMR in chiral liquid crystals (CLC) to access their enantiopurity ratios.<sup>6</sup>

In this work, we propose to replace the tritium atom of the chiral methyl group by a methyl moiety to obtain the non-radioactive ethyl chiral group. After the achievement of the first chemical synthesis of such crypto-optically active probes with a high deuterium atom incorporation,<sup>7</sup> to completely describe each enantiomer, modern analytical techniques were used (Figure 1). It is important to note that some alkyl transferase enzymes tolerate various alkyl groups as ethyl, allyl or propargyl during the transfer process,<sup>8</sup> and so chiral ethyl probes could be helpful for studies of this class of enzymes. As a matter of fact, radioactive chiral ethyl group has already been used for the understanding of enzymatic mechanisms.<sup>9</sup>

Our synthetic approach to the chiral ethyl group was inspired by the one described by Hammerschmidt *et al.* for the synthesis of chiral methyl tosylate<sup>10</sup> (Scheme 1). First, the chloromethyldimethylphenylsilane **1** was converted to the corresponding alcohol **2** in good yield. Then, carbamate **3** was



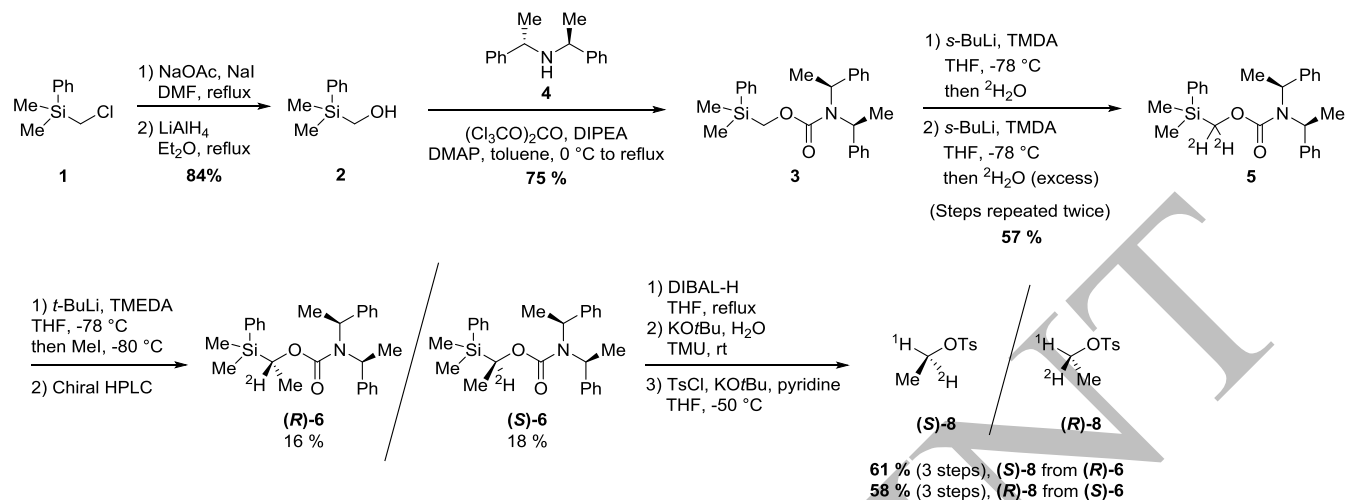
**Figure 1.** Goals of this work.

obtained by the condensation of bis-((*S*)-1-phenylethyl)amine **4** with triphosgene followed by the addition of alcohol **2**. Carbamate **3** was then deuterated in the  $\alpha$ -position of the silicon atom via two consecutive lithiation/deuteration sequences allowing a  $^2\text{H}$  incorporation over 99%. Then, the di-deuterated carbamate **5** was alkylated using iodomethane through an optimized lithiation process (Table S1 for optimization). The use of *t*-BuLi at  $-50\text{ }^\circ\text{C}$  (Table S1, entry 4) led to a mixture of diastereoisomers **6** (Scheme 1) with a high conversion. Then the two diastereoisomers were separated using chiral HPLC. Treatment of mono-deuterated **6** with DIBAL-H cleaved the carbamate moiety to give the corresponding chiral alcohol (not isolated due to its high volatility). A consecutive Brook rearrangement followed by the tosylation of the ethanol intermediate gave chiral ethyl tosylates **8**.

As the determination of the absolute configuration (AC) is an essential information for the use of such chiral molecules as probes,<sup>11,12</sup> combination of several modern analytical methods for the characterization of isotopic chirality have been described. First, in 2007, X-ray crystallography and vibrational circular dichroism (VCD) were used to determine the AC of (*R*)-4-ethyl-4-methyloctane.<sup>13</sup> Then, quantum chemical (QC) computations have been coupled with Raman optical activity (ROA)<sup>14</sup> or VCD<sup>15,16,17</sup> experiments to provide essential information on various crypto-optically active compounds. During our whole synthetic pathway, no information regarding the *ee* and AC could be obtained by optical rotation, so VCD analysis was performed.<sup>18</sup> Figure 2a (top) reveals mirror image signals for enantiomers (for complete VCD spectra, see Figure S17). The most relevant signatures were observed between  $1000$  and  $1050\text{ cm}^{-1}$  and between  $1250$  and  $1350\text{ cm}^{-1}$ . To assign signals to products, QC calculations were performed (Figures 2b (top)) and then calculated and experimental IR and VCD spectra were compared (Figures 2b and 2c). The M06-2X-based frequencies were scaled down by a factor of 0.9725, giving the maximum similarity with the experimental VCD and IR spectra. Interestingly note that although [ $^2\text{H}$ ]-ethyl tosylate **8** is called crypto-optically active, it actually displays a VCD activity.

A comparison using B3LYP functional (Figures S19 and S20) shows that M06-2X gives better agreement to experiment overall. The VCD band signs predicted for (*S*)-stereoisomer appear clearly opposite to those seen for (*R*)-**8**. Therefore, both level calculations enabled to confirm the AC of (*R*)-**8** and (*S*)-**8** enantiomers in relation with the signs of the VCD signals (Figure 2). It is interesting to note that the corresponding *S*-(-) and *R*-(+)

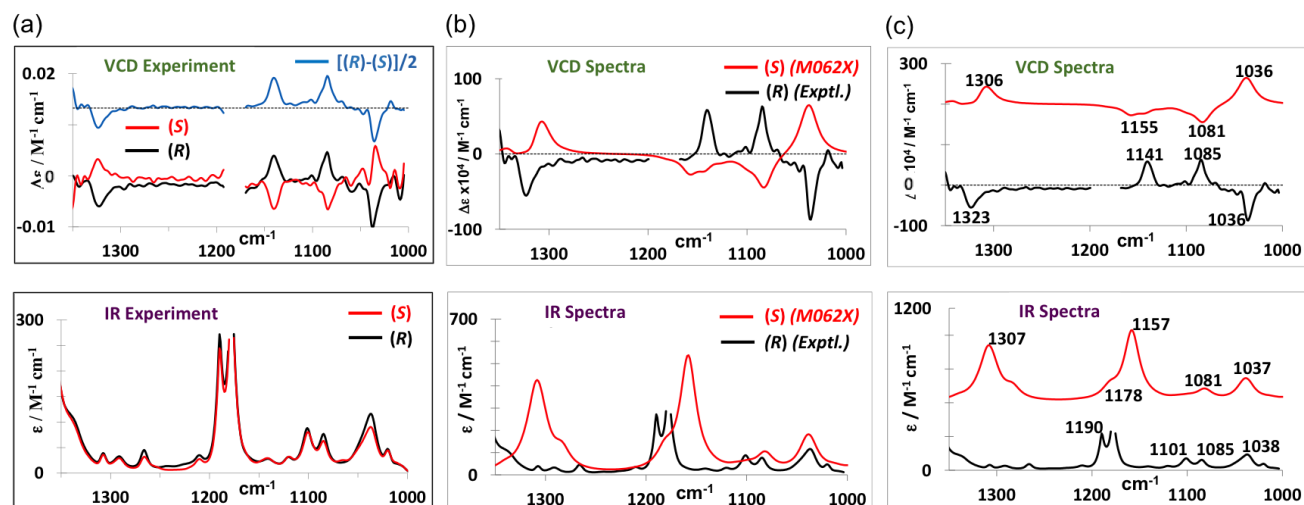
AC of [1- $^2\text{H}_1$ ]ethanol were determined by three methods (enzymatic,<sup>19</sup> chemical correlation from sugars,<sup>20</sup> and VCD<sup>21</sup>).



**Scheme 1.** Synthesis of deuterated crypto-optically active probes (*R*)-**8** and (*S*)-**8**.

Finally, the isotopic enantiomers of **8** were studied with the help of  $^2\text{H}$ - $\{^1\text{H}\}$  2D NMR recorded at 92.1 MHz and 297 K in the PBLG-based chiral mesophase (20.7%  $m_{\text{PBLG}}/m_{\text{tot}}$ ). In such lyotropic CLCs, each monodeuterated enantiomer generates a single  $^2\text{H}$  quadrupolar doublet ( $^2\text{H}$ -QD) when the spectral enantiodiscrimination occurs;<sup>6</sup> two  $^2\text{H}$ -QD are therefore theoretically expected if the *R/S*  $^2\text{H}$ -signals are resolved. This occurrence has been observed on  $^2\text{H}$ - $\{^1\text{H}\}$  2D-NMR spectrum recorded at natural abundance deuterium (NAD) level of commercial ethyl tosylate when DMF is used as organic co-solvent (Figure 3a and S22) In this case, each monodeuterated enantio-isotopomer ((*S*)- $\text{C}^*\text{DH}$ - and (*R*)- $\text{C}^*\text{HD}$ -) associated with the pro-(*S*) and pro-(*R*) hydrogenated enantiotopic position are detected. Note that using chloroform, a weakly polar co-solvent, no spectral enantiodiscrimination occurs.<sup>6b,c</sup>

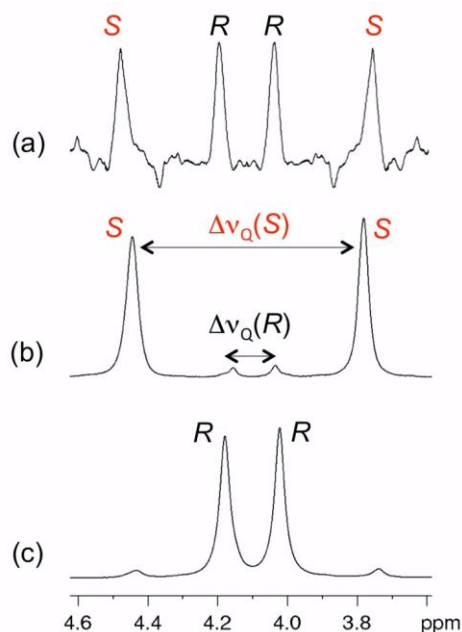
The enantiopurity of the two isotopically-labeled compounds **8** (Figure 3b,c) has been determined at the same T (297 K) and using identical PBLG mass ratio (20.9%), thus leading to a magnitude of  $^2\text{H}$  splittings identical to those observed on the anisotropic NAD NMR spectra. The large difference in



**Figure 2.** (a) Solvent-subtracted experimental VCD (top panel) and (bottom panel) and IR spectra of (*S*)-8 (red) and (*R*)-8 (black) in the 1350-1000 cm<sup>-1</sup> region measured in CD<sub>2</sub>Cl<sub>2</sub> solvent. The top most trace (blue), obtained as one-half of the difference between VCD spectra of *R* and *S* enantiomers, gives the VCD spectrum of (*R*)-8 with improved S/N ratio (slightly shifted upwards for clarity). VCD spectra in the 1168-1198 cm<sup>-1</sup> region, and IR peak at ~1178 cm<sup>-1</sup>, is not displayed due to noise associated with excessive absorbance. (b) Comparison of the experimental VCD and IR spectra for (*R*)-8 (black traces) and the predicted spectra for the (*S*)-enantiomer at the M06-2X/6-311++G(2d,2p) level (red traces). (c) The spectra in the panel (b) are shifted upwards and stacked above each other for displaying the peak positions. All calculated frequencies are scaled by a factor of 0.9725. Note that the strongest IR band around 1180 cm<sup>-1</sup> has been truncated since strong absorption may induce artefacts.

intensity between each <sup>2</sup>H-QD of (*S*)-8 and (*R*)-8 reveals the presence of a significant enantiopurity. Deconvolution of the signals indicates that the chiral ethyl tosylate was prepared with an *ee* greater than 90% for both isomers.

**In conclusion, the first chemical synthesis of non-radioactive chiral ethyl group, was developed. While the anisotropic <sup>2</sup>H NMR allowed enantiopurity evaluation, the VCD analysis / QC calculations combination permitted to assign the AC of each synthesized enantiomer of the chiral ethyl tosylate. Due to their easier synthetic access and handling compared to their radioactive counterparts such small crypto-optically active probes possess a great potential of applications to decipher alkyl transferase enzymes reaction mechanisms.**



**Figure 3.** (a) NAD  $^2\text{H}\{-^1\text{H}\}$  1D-NMR projection (sum of columns) extracted from the tilted and symmetrized  $Q$ -resolved Fz 2D experiment (details in SI) of racemic ethyl tosylate (42 mg), PBLG (130 mg), DMF (450 mg). (b) and (c): Same as (a) but obtained with (**S**)-**8** and (**R**)-**8**, respectively (5 mg of labeled plus 35 mg of unlabeled ( $R/S$ )-solute), PBLG (130 mg), and DMF (452 mg). The degree of polymerization (DP) of PBLG is equal to 710.

### Supporting information:

Experimental procedure details, NMR data for compounds **2** to **8**, QC calculation, anisotropic  $^2\text{H}$  NMR analysis (PDF)

### Authors information:

The authors declare no competing financial interest.

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