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LETTER

Chiral Discrimination of β-Telluride Carboxylic Acids by NMR Spectroscopy

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In this work the nuclei (^{1}H and ^{125}Te) for NMR spectroscopy and enantiopure compounds as chiral solvent agent (CSA) and chiral derivatisating agent (CDA) were evaluated in different conditions. The structure of β-telluride carboxylic acids was also modified to observe the effect on anisochrony.

The development and applications of organic tellurium compounds has expanded in recent years.[1] Among the several applications in organic chemistry, their use in total synthesis[2] and as fragments of biologically active compounds[3] is certainly the most highlighted. Furthermore, the organic tellurium compounds can be prepared as highly stereoselective by the hydrotelluration reaction of alkynes,[4] and the reactivity enables several possibilities of carbon-carbon bond formation by transmetalation reactions and cross-coupling reactions.[5] The use of organotellurides as a source of reactive organometallics has been considered an efficient tool for synthetic organic chemistry.[2,5,6]

Recently, we described an efficient methodology for the preparation of γ, δ□and ε telluride carboxylic acids by a lactones ring opening reaction.[7] The aim of this previous work was to prepare chiral organotelluride carboxylic acids since the synthesis of chiral organic tellurium compounds still remains underexplored.[8] However, our attempts to perform the chiral discrimination of these compounds by chromatographic methods (GC and HPLC) failed. The telluride carboxylic acids degraded because of the analysis conditions and the long retention time. The instability of some organic tellurium compounds is known,[7] mainly of alkyl tellurides.[9]

In this way, and following our current interest in ^{77}Se and ^{125}Te NMR spectroscopy,[10] we decided to investigate the chiral discrimination of β-organotelluride carboxylic acids by NMR spectroscopy. Nuclear magnetic resonance spectroscopy is one of the most efficient methods used to determine optical purity and assign the absolute configuration of chiral compounds.[11] Based on the features of organotelluride carboxylic acids and to eliminate the use of covalent derivatisations, the development of a chiral derivatisation protocol that is facile, rapid, and under mild conditions, would be ideal to enable the enantiomeric excess (ee) by NMR. The advantage of using non-covalent chiral solvating agent (CSA) relies on the possibility of carrying out the experiment *in situ*, without additional steps. Moreover, there is an increasing number of papers describing CSAs for carboxylic acids,[12] making it a practical and readily available method.

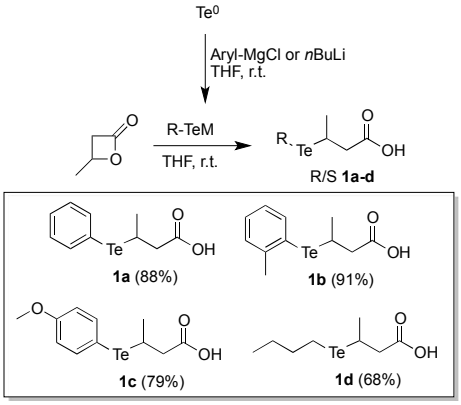
In this communication, we wish to report a simple *in situ* approach for chiral discrimination of β-telluride carboxylic acids by ^{1}H and ^{125}Te NMR spectroscopy. Moreover, regarding the greater challenges for the determination of the absolute configuration and chiral discrimination of β-hetero groups by NMR spectroscopy,[11c,13] this study provides an experimental basis for application in other β-hetero-organic groups.

The β-telluride carboxylic acids **1a-d** were readily prepared by a ring opening reaction of β-butyrolactone through the soft nucleophilicity of organotellurolate anions (Scheme 1). The products were achieved in good yields (Scheme 1; 68–91%). The preparation *in situ* of organotellurolates avoids unpleasant smells and decreases the number of steps. The β-telluride carboxylic acids obtained when in a solution and in presence of air rapidly decomposes, forming a white amorphous solid. These organic tellurium compounds should be kept at low temperatures.

Initially, we decided to employ the ^{125}Te NMR for chiral discrimination. The reasonably natural abundance of ^{125}Te (6.99%), and with a chemical shift range of about 7000 ppm, makes ^{125}Te an excellent nucleus for NMR research.[14] Menezes *et al.* performed this method for organoselenenides carboxylic acids, employing ^{77}Se NMR, with great success.[15]

Several ^{125}Te NMR experiments were attempted with different quantities of (+)-methylbenzylamine – [(+)-MBA] as a chiral solvating agent (Figure 1). ^{125}Te NMR spectra were acquired in a 300 MHz spectrometer. The β-telluride carboxylic acid **1a** was added to an NMR tube, and the ^{125}Te NMR spectrum was recorded (Figure 1: δ 709 ppm). The amount of (+)-MBA was gradually increased at 25°C and the ^{125}Te NMR spectrum was recorded after each increment. The chemical shift (δ ppm) changed upfield gradually in the presence of (+)-MBA. Figure 1 shows no separation,

and the determination of enantiomer composition failed. The ^{125}Te NMR shifts observed are thus average shifts of the solvated and unsolvated species. Further additions of (+)-MBA do not change the chemical shift or signal resolution. The temperature was lowered to 0°C, but the anisochrony improvements were not enough to observe the peaks of both diastereomers complexes.



Scheme 1 Ring opening reaction of β-butyrolactone by organotellurolates

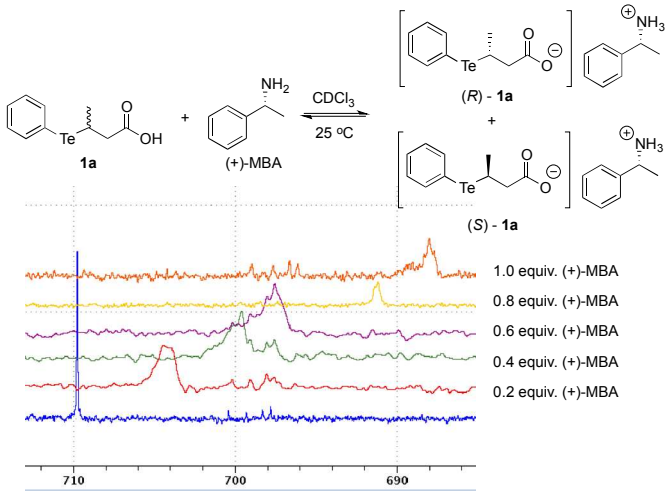


Figure 1 ^{125}Te NMR spectra of carboxylic acid **1a** for chiral discrimination using different amounts of (+)-MBA at 25°C

In this way, the (+)-MBA was used as covalent chiral derivasation agent. For this proposal, a reaction of β-telluride carboxylic acid **1a** with (+)-MBA and DIC (*N*,*N*'-diisopropylcarbodiimide) was performed in an NMR tube (Figure 2). The reagents were added to an NMR tube and mixed for 10 minutes. After this time, a ^{125}Te NMR spectrum was recorded. Figure 2 shows a separation of 1.62 ppm (153 Hz) due a two diastereomers formed. In this case, there is no dynamics between the compounds obtained and reagents, allowing to observe both signals. The reaction performed with DCC (*N*,*N*'-dicyclohexylcarbodiimide) gave some particles in a NMR tube decreasing significantly the resolution of the experiments. The reaction carried out in other solvents (C_6D_6 and AcCN-d_3) did not obtain good yields.

After these results, we turned our attention to ^{1}H NMR spectroscopy. In this set of experiments, the NMR chiral discrimination was carried out by mixing equimolecular amounts of the corresponding β-telluride carboxylic acid **1** and (+)-MBA in deuterated solvent (10 mM) at 25°C (Table 1). The change in the position of the chemical shift was designated as $\Delta\delta$ and the differences in the separated peaks in terms of chemical shift non-equivalences were designated by $\Delta\Delta\delta$ (ppm and Hz). ^{1}H NMR spectra were acquired in a 500 MHz spectrometer.

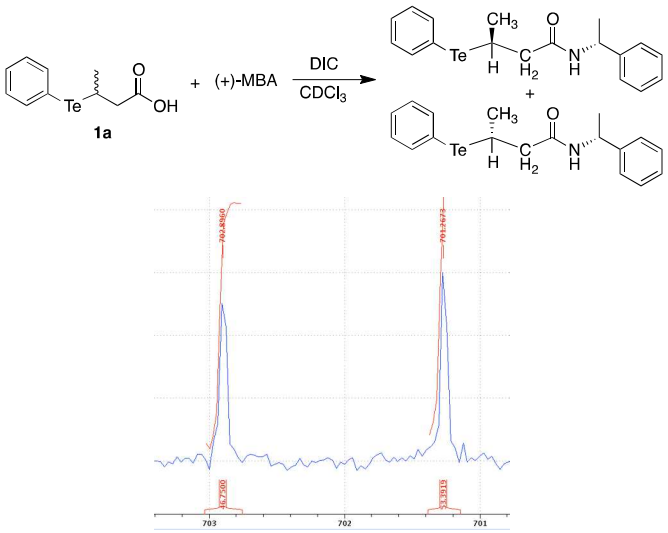


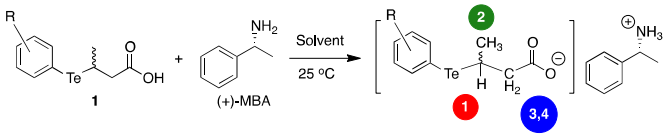
Figure 2 ^{125}Te NMR Chiral discrimination of β-telluride carboxylic acid **1a** by reaction with DIC and (+)-MBA in an NMR tube.

Immediately after the addition of (+)-MBA and β-telluride carboxylic acid **1a** in $CDCl_3$, the splitting between signals was observed (Table 1; Entry 1; $\Delta\Delta\delta$ = 0.0047 ppm). There was very little observed chemical shift difference because the chiral centre is further away (β-position). Thus, the next step is to perform the optimisation of NMR conditions to improve the anisochrony (Table 1). The different polarities of solvents were investigated for chiral discrimination. The benzene-d_6 solvent led to the largest splitting values (Table 1; Entries 2, 8 and 11). We observed that nonpolar solvents tended to increase the anisochrony since acetone-d_6 and CD_3CN compete to form hydrogen bond with (+)-MBA. The displacement of the aromatic ring to the aliphatic (*n*-butyl) group in the tellurium fragment ended the anisochrony (Table 1; Entries 12 and 13). When the chalcogen atom was replaced from tellurium to selenium in the compound **1a**, the difference in the magnetic environment generated by the diastereomeric complex occurred in the signal 3 (Figure S20, CH_2 group / $\Delta\Delta\delta$ = 0.0056 ppm—supplementary information).

The present protocol has the capability of chiral discrimination by ^{1}H NMR; nevertheless, improvements are needed to increase the difference in the chemical environment in both the diastereomers. For this purpose, the search for an effective chiral solvent agent is required. In many cases, the CSAs require a multistep synthesis limiting their routine practical applicability, thus, our goal is to use readily available chiral organic compounds.

At first, we selected the β-telluride carboxylic acid **1c** for a standard comparison. Our first attempt was to use the acetamide prepared from (+)-MBA as CSA. The positive and negative sites in the amide moiety provide points for dipole-dipole interactions, but the splitting value decreased (Figure S24, $\Delta\Delta\delta$ = 0.0022 ppm—supplementary information). The subsequent attempt was to use a chiral diamine. These compounds are used as a chiral NMR solvating agent for a variety of carboxylic acids, sulfonic acids and β-diketones.[12a,16] The diamine (*S*,*S*)-**2a** was synthesised by Eames's procedure (see supplementary information).[17] However, the diamine (*S*,*S*)-**2a** was ineffective in distinguishing hydrogen atoms of the β-telluride carboxylic acid **1c** enantiomers.

Table 1 ^{1}H NMR chiral discrimination of β-telluride carboxylic acids **1a-d** with (+)-MBA.[a]



Entry	Acid	Solvent	Signal	Δδ ppm	ΔΔδ ppm	ΔΔδ Hz
1	**1a**	$CDCl_3$	2	- 0.116	0.0047	2.35
2	**1a**	C_6D_6	2	+ 0.218	0.0062	3.10
3	**1a**	DMSO-d_6	2	- 0.260	0.0045	2.25
4	**1a**	D_3COCD_3	----	----	----	----
5	**1a**	CD_3CN	----	----	----	----
6	**1b**	DMSO-d_6	2	- 0.243	0.0059	2.95
7[b]	**1b**	$CDCl_3$	----	----	----	----
8	**1b**	C_6D_6	2	+ 0.232	0.0087	4.35
9	**1c**	DMSO-d_6	2	- 0.146	0.0024	1.20
10[b]	**1c**	$CDCl_3$	----	----	----	----
11	**1c**	C_6D_6	2	+ 0.219	0.0046	2.30
12	**1d**	$CDCl_3$	----	----	----	----
13	**1d**	C_6D_6	----	----	----	----

[a] An equimolecular amount of (+)-MBA and carboxylic acid **1** were diluted in the respective deuterated solvent (10 mM) at 25°C; [b] Overlap signals.

Alternatively, Bedekar *et al.* used aminophthols for NMR solvating agents for chiral discrimination of racemic mandelic acid.[18] Aminonaphthols and their derivatives exhibit an important role in organic chemistry regarding the easy access to chiral molecules by a Betti condensation reaction.[19] The aminonaphthol **3a** was prepared by a three component aromatic Mannich reaction (see supplementary information). The *O*-benzyl-aminonaphthol **3b** was prepared by a one-pot *O*-alkylation reaction. The aminonaphthols **3a** and **3b** were examined as a chiral NMR solvating agent (Table S1: supplementary information). The aminonaphthol **3a** was not able to perform the chiral discrimination of the β-telluride carboxylic acid **1c** in different solvents. The aminonaphthol **3b** was effective in the NMR chiral discrimination and the separated peaks showed a lower value than (+)-MBA.

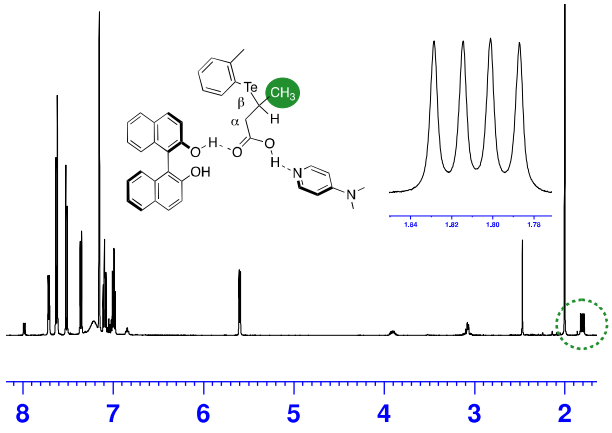


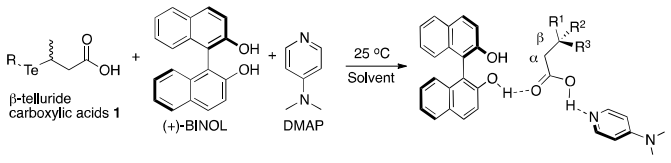
Figure 3 ^{1}H NMR Chiral discrimination of β-telluride carboxylic acid **1b** by BINOL/DMAP methodology.

In order to overcome these results, we decided to use (+)-BINOL, another readily available compound for enantioselective molecular recognition (Figure 3). Chiral 1,1-Bi-2-naphthol (BINOL) is a very efficient and versatile probe for diverse analytical methods.[20] Moreover, the BINOL does not contain any aliphatic protons avoiding signal overlap problems. In spite of these characteristics, we employed Suryaprakask's methodology for NMR chiral discrimination.[21] The procedure uses (+)-BINOL and a base (*N*,*N*-dimethylpyridin-4-amine, DMAP) for interaction improvements.

Table 2 shows the results of NMR chiral discrimination by ternary ion-par complex formation. The separation in the chemical environment for diastereomers complex was effective just for benzene-d_6 solvent, unlike Suryaprakask's work where chloroform showed better results.[21a] The splitting value of the peaks obtained was greater than (+)-MBA and aminonaphthol **3b** enabling an accurate measurement of the signals. The change in the position of the chemical shift (Δδ was downfield in all NMR chiral discriminations.

Once more, it is possible to observe the effect of the aromatic ring of β-telluride carboxylic acid on anisochrony (Table 3, Entries 2, 5 and 6). The BINOL/DMAP approach was also effective for β-telluride carboxylic acid **1d** (Table 3, Entry 7). Further additions of DMAP (1.4 and 1.6 equiv.) do not change the chemical shift or signal resolution. The use of only (+)-BINOL was not able to perform the chiral discrimination by NMR.

Table 2 Ternary ion-pair complex formation for NMR chiral discrimination of β-telluride carboxylic acids **1a-d** with (+)-BINOL/DMAP at 25°C.[a]



Entry	Acid	Solvent	Signal	Δδ ppm	ΔΔδ ppm	ΔΔδ Hz
1	**1c**	$CDCl_3$	----	----	----	----
2	**1c**	C_6D_6	2	+ 0.341	0.0216	10.8
3	**1c**	CD_3CN	----	----	----	----
4	**1c**	DMSO-d_6	----	----	----	----
5	**1a**	C_6D_6	2	+ 0.425	0.0210	10.5
6	**1b**	C_6D_6	2	+ 0.163	0.0274	13.7
7	**1d**	C_6D_6	2	+ 0.145	0.0101	5.1

[a] An equimolecular amount of (+)-BINOL/DMAP and carboxylic acid **1** were diluted in the respective deuterated solvent (10 mM) at 25°C.

All chiral solvating agents used showed a clear trend for greater NMR chiral discrimination of β-telluride carboxylic acids using benzene-d_6 as solvent. The tellurium fragment increases the liposolubility of carboxylic acids enhancing the non-polar interactions. In addition to this fact, we applied a simple deconvolution to show that even the least efficient chiral solvating agents can be successfully employed for NMR chiral discrimination of β-telluride carboxylic acids without additional NMR experiments (see supplementary information). The method based on reaction with β-telluride carboxylic acid with (+)-MBA and DIC was not able to perform the chiral discrimination by ^{1}H NMR because the signal overlapping with byproducts.

In summary, the (+)-BINOL/DMAP protocol has shown an efficient ^{1}H NMR chiral discrimination by chiral solvent agent (CSA) in benzene-d_6 as solvent at 25°C of β-telluride carboxylic acids. Different probes were evaluated as CSA, and together with the tool deconvolution, can be applied in order to obtain accurate results. The reaction between β-telluride carboxylic acid, (+)-MBA and DIC represents an effective method for ^{125}Te NMR chiral discrimination.

NMR chiral discrimination is a powerful tool for assessing unstable and high molecular weight compounds, and jointly with simple protocols, represents an efficient alternative to chromatographic and related separation methods. Further investigations of exploring NMR chiral discrimination and the synthesis of chiral carboxylic acids containing tellurium atom are underway in our laboratory.

Experimental

Deuterated solvents (99.9% purity with 0.03 % vv of TMS) were purchased from Sigma Aldrich®. Either 300 MHz or 500 MHz acquired the ^{1}H, ^{13}C and ^{125}Te NMR spectra. The model of NMR equipment – 300MHz Avance III Bruker equipped with a direct BBO probe (broad-band-observed) and 500MHz Avance III Bruker equipped with an inverse TXI probe (triple-resonance-inversed). The chemical shifts of ^{1}H NMR are reported in parts per million (ppm) relative to tetramethylsilane (TMS) peak (δ 0.0 ppm) and coupling constant (J) in Hertz and integrated intensity. The chemical shifts of ^{13}C NMR are reported in ppm relative to $CDCl_3$ signal (δ 77.0 ppm). The chemical shifts of ^{125}Te NMR are reported in ppm relative to internal standard $C_6H_5TeTeC_6H_5$ (δ 422 ppm).

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Notes and references

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† Electronic Supplementary Information (ESI) available: General experimental procedure and NMR spectra. See DOI: 10.1039/c000000x/

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A simple and effective procedure for chiral discrimination of β-telluride carboxylic acids by ^{1}H and ^{125}Te NMR spectroscopy is presented