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NMR chiral discrimination of chalcogen containing secondary alcohols

Naiade B.G. Marques[2] | Raquel G. Jacob[1] | Gelson Perin[1] | Eder J. Lenardão[1] | Diego Alves[1] | Márcio S. Silva[1,2]

[1]Laboratório de Síntese Orgânica Limpa (LASOL), Centro de Ciências Químicas, Farmacêuticas e de Alimentos (CCQFA), Universidade Federal de Pelotas (UFPel), Capão do Leão, Brazil

[2]Laboratório de Ressonância Magnética Nuclear, Centro de Ciências Naturais e Humanas (CCNH), Universidade Federal do ABC, Santo André, Brazil

Correspondence
Márcio Santos Silva, Laboratório de Síntese Orgânica Limpa (LASOL), Centro de Ciências Químicas, Farmacêuticas e de Alimentos (CCQFA), Universidade Federal de Pelotas (UFPel), Capão do Leão, RS, Brazil.
Email: silva.ms@ufpel.edu.br

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Abstract

Here, we report the general strategies by which NMR spectroscopy can be used to determine the enantiopurity and absolute configuration of chalcogen containing secondary alcohols, including the evaluation of the use of chiral solvating and chiral derivatizing agents. The BINOL/DMAP ternary complex demonstrated a simple and fast protocol for determining enantiopurity. The drug Naproxen afforded a stable, nonhygroscopic, and readily available chiral derivatizing agent (CDA) for NMR chiral discrimination of chalcogen containing secondary alcohols. The chiral recognition by CDA and chiral solvating agent (CSA) was assessed using ^{1}H, ^{77}Se-{1H}, and ^{125}Te-{1H} NMR spectroscopy. A simple model for the assignment of the absolute configuration from NMR data is presented.

KEYWORDS

chalcogen compounds, chiral derivatizing agent, chiral solvating agent, NMR discrimination, secondary alcohols

1 | INTRODUCTION

Nuclear magnetic resonance (NMR) spectroscopy is a consolidated analysis used to evaluate the enantiopurity and the assignment of absolute configuration of organic compounds.[1-4] The procedure relies on the use of an enantiomerically pure reagent that causes an anisotropic effect, which is predictable in the NMR spectrum. The NMR recognition of secondary alcohols is commonly done by derivatization with methoxytrifluoromethylphenylacetic acid (MTPA), methoxyphenylacetic acid (MPA), or 9-anthrylmethoxyacetic acid (9-AMA) chiral auxiliaries.[5] However, these reagents have some problems, including low reactivity,[6] possible racemization,[7] being highly hygroscopic, and very small $\Delta\delta^{RS}$ values.[8] Consequently, the choice of chiral auxiliary is an important strategy for NMR chiral recognition of secondary alcohols.

Among the different chiral reagents, Naproxen is a stable, nonhygroscopic, and readily available chiral carboxylic acid. Satisfactory results for NMR chiral discrimination are presented in the literature, such as phosphine oxides by Naproxen as a chiral solvating agent (CSA)[9] and aminophosphonates by Naproxen chloride as a chiral derivatizing agent (CDA).[10]

NMR analysis using CSAs can often involve a trial-and-error approach, and huge differences can occur because of

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the molecular structure and/or functional group.[11] However, the practicality, and low time-consuming, to employ a CSA, usually emerges as a desired alternative.

On the other hand, organic chalcogen (Se and Te) compounds are versatile synthetic intermediates for the synthesis of complex molecules.[12,13] Furthermore, compounds containing chalcogen atoms have demonstrated a wide scope of pharmacological activities.[14-16] Thus, the use of chiral organochalcogen compounds represents a great opportunity for increasing the range of synthetic intermediates[17] and bioactive compounds.[18] Among the methods used to obtain chiral chalcogen containing secondary alcohols, biocatalytic methods have exhibited a high effectivity.[19]

Considering the importance of organochalcogen compounds and secondary alcohol derivatives, and due to the possibility of exploring ^{77}Se and ^{125}Te NMR spectroscopy to study chirality, we report a method for NMR chiral discrimination and NMR assignment of the absolute configuration of chalcogen containing secondary alcohols. Our strategy involves the use of the 1,1′-bi-2-naphthol and 4-(dimethylamino) pyridine (BINOL/DMAP) ternary complex as a CSA and Naproxen as a CDA.

2 | MATERIALS AND METHODS

2.1 | Nuclear magnetic resonance

^{1}H, ^{77}Se-{^{1}H}, and ^{125}Te-{^{1}H} spectra of Naproxen esters derivatives were recorded using an NMR spectrometer with 300 or 500 MHz (Bruker, Avance III model). The probe was a 5-mm direct broadband observe (BBO) z-gradient from 300 MHz and 5-mm indirect TXI z-gradient from 500 MHz. Spectra were recorded in deuterated chloroform, deuterated pyridine, and deuterated benzene (5-mm tubes) at 298 K. The data reported includes chemical shift (δ), multiplicity, coupling constant (J) in hertz, and integrated intensity. The ^{77}Se NMR chemical shifts are reported in ppm relative to the internal standard $C_6H_5SeSeC_6H_5$ (δ 463 ppm). The ^{125}Te NMR chemical shifts are reported in ppm relative to the internal standard $C_6H_5TeTeC_6H_5$ (δ 422 ppm). The parameters of ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} NMR spectroscopy were 0.34 second of acquisition time, 1.0 second of relaxation time, 12.0 microseconds of pulse width, 2048 sans, and 3.0 of line broadening, and the baseline correction was carried out manually. The NMR pulse sequence employed for ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} experiments was gated decoupling.

2.2 | Chemicals

Chiral auxiliaries (MTPA, BINOL, MPA, mandelic acid, Naproxen), deuterated benzene (C_6D_6), deuterated pyridine (Py-d_5), deuterated chloroform ($CDCl_3$), *N*,*N*′-diisopropylcarbodiimide (DIC), and *N*,*N*′-dicyclohexylcarbodiimide (DCC) were purchased from Sigma-Aldrich, Brazil.

2.3 | General procedure for the synthesis of racemic chalcogen containing secondary alcohols

The racemic chalcogen (Se and Te) containing secondary alcohols **1** were synthesized and characterized as recently described.[20] To a 5-mL vial equipped with a magnetic stirrer and rubber septum under nitrogen, dialkyl or diaryl dichalcogenide (0.5 mmol) and the epoxy (1.5 mmol) were added, followed by the catalyst system ($NaBH_4$/Al_2O_3, 1.0 mmol/50 mg). The mixture was then stirred for 120 minutes at 50 °C. The reaction progress was monitored by thin layer chromatography (TLC) and gas chromatography (GC). After 20 minutes at room temperature, the reaction medium was diluted with AcOEt (20 mL) and washed with a saturated aqueous solution of NH_4Cl (15 mL). The phases were separated, and the aqueous phase was extracted with AcOEt (2 × 20 mL). The organic phase was dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The product was purified by flash column chromatography, eluting first with hexane to remove the dialkyl or diaryl dichalcogenides by-products and then with hexane/AcOEt (8:2) to remove the secondary chalcogen alcohol.

2.4 | General procedure for NMR chiral discrimination of racemic and chiral chalcogen containing secondary alcohols

CSA

Samples for NMR spectroscopy were prepared by weighing and dissolving the appropriate amount of chalcogen alcohol **1**, chiral auxiliary, and base in the respective deuterated solvent to prepare a 20 mM solution. The solutions were shaken for 2 minutes for equilibration time.

CDA

Samples for NMR spectroscopy were prepared weighing and dissolving 0.05 mmol of chalcogen alcohol **1**, 0.05 mmol of Naproxen, and 0.05 mmol of DCC in 600 μL of $CDCl_3$. The solutions were shaken for 10 minutes. A white solid is obtained. After 30 minutes, the white solid is decanted, and the NMR spectra were recorded. The solutions were prepared in a vial or directly

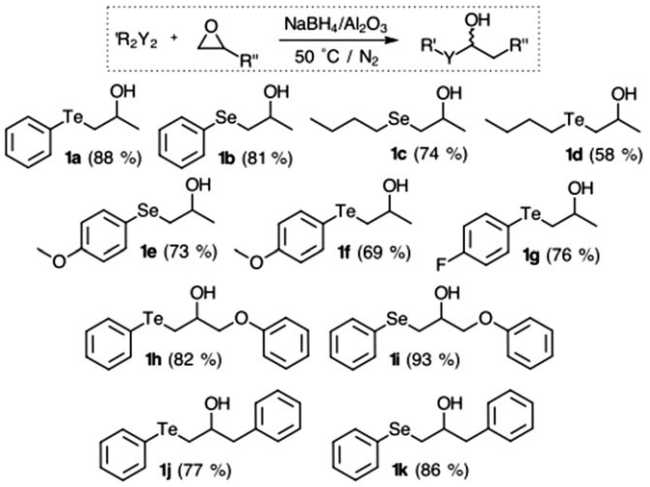
in an NMR tube. Usually, the vials were the best option due the absence of the white solid in the NMR tube, and by the possibility to use a centrifuge equipment for faster decantation.

3 | RESULTS AND DISCUSSION

3.1 | Chiral solvating agent

The study began with the synthesis of racemic chalcogen containing secondary alcohol **1**. The synthesis was carried out using a simple and nonconventional method based on the solid support $NaBH_4/Al_2O_3$ (Scheme 1).[20] This atom-economic strategy involves the ring-opening reaction of epoxides by nucleophilic species of chalcogenides. Moreover, this simple procedure does not involve harsh reaction conditions and is not time-consuming. The yields were moderate to satisfactory (Scheme 1).

After the synthesis of secondary chalcogen containing secondary alcohol **1**, chalcogen alcohol **1a** was chosen as a substrate model for optimization of the NMR chiral discrimination. Initially, different CSAs were evaluated due to the readiness of the method. By combining 1.0 equivalent of (+)-MTPA, (+)-MPA, (+)-mandelic acid, (+)-BINOL, or (+)-Naproxen with chalcogen alcohol **1a** in $CDCl_3$, the desired anisotropic effect was not observed in the ^1H and ^{125}Te-{^1H} NMR spectra. Based on the formation of a ternary complex[21] and to improve the intermolecular interactions, 1.0 equivalent of 4-(dimethylamino) pyridine (DMAP) base was added to the medium with the CSA. In this protocol, the split signals in the ^1H NMR spectrum was observed only with (+)-BINOL/DMAP ternary complex. The ^{125}Te-{^1H} NMR experiment recorded did not show anisotropy of the tellurium atom.



SCHEME 1 Synthesis of racemic chalcogen containing secondary alcohol **1**

Regarding the strong influence of physical parameters on the CSA interaction, the solvent and the substrate were modified to evaluate the performance of the NMR chiral discrimination by the (+)-BINOL/DMAP ternary complex. To verify the influence of the substrate, different chalcogen alcohols **1** were tested (Table 1). The ^{77}Se-{^1H} NMR experiments recorded did not show an anisotropic effect, and the ^1H NMR experiments gave the same results (Table 1, entries 3, 4, and 5). As can be seen in Table 1, the presence of deuterated benzene improved the anisotropic effect (Table 1, entries 2, 4, 5, and 6). An excess of DMAP (2.0 and 3.0 equiv.) did not demonstrate improvements.

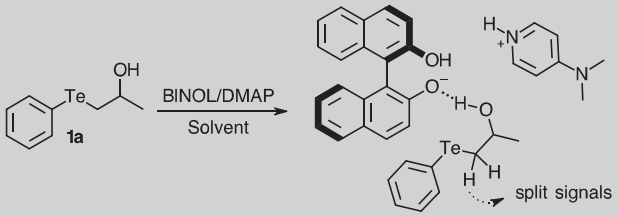
The protocol demonstrates a good baseline resolution and faster chiral discrimination procedure. In an attempt to improve the $\Delta\delta^{RS}$ values of the CSAs obtained and to access the absolute configuration, the CDA methodology was evaluated.

3.2 | Chiral derivatizing agent

After the CSA results, the chiral carboxylic acids ((+)-MTPA, (+)-MPA, and (+)-Naproxen) were evaluated as CDAs for NMR chiral discrimination. Initially, the reaction was performed using 0.25 mmol of chalcogen alcohol **1a**, 0.25 mmol of DIC, and 0.25 mmol of the chiral carboxylic acid, using 2 mL of CH_2Cl_2 as the solvent at 30 °C under magnetic stirring (Table 2). The desired product was obtained in 78% yield after 30 minutes with (+)-Naproxen chiral auxiliary. The reaction with (+)-MTPA did not work after 24 hours of reaction time. The reaction with (+)-MPA afforded a lower yield after 24 hours. Thus, the split signal of the enantiomers was obtained only with (+)-Naproxen, and the ^1H and ^{125}Te-{^1H} NMR experiments showed substantial $\Delta\delta^{RS}$ values (Table 2, entries 5 and 6). To improve this result, DCC was employed instead of the DIC coupling reagent. When the reaction was performed with chalcogen alcohol **1a**, DCC, and (+)-Naproxen, the yield increased to 87%. The reaction of chalcogen alcohol **1a** with DCC and (+)-MPA or (+)-MTPA did not work after 24 hours of reaction time.

After DCC was defined as the best coupling reagent for the reaction between carboxylic acids and chalcogen containing secondary alcohols to obtain diastereomeric esters, the deuterated solvent was evaluated. By using deuterated benzene, there was an improvement in the $\Delta\delta^{RS}$ value of the ^{125}Te-{^1H} NMR (Table 3, entry 1). However, the $\Delta\delta^{RS}$ value of the ^1H NMR spectrum decreased significantly (Table 3, entry 2). Inversely, the

TABLE 1 ^{1}H (500 MHz) NMR chiral discrimination of chalcogen containing secondary alcohol **1** by the (+)-BINOL/DMAP ternary chiral complex[a,b]



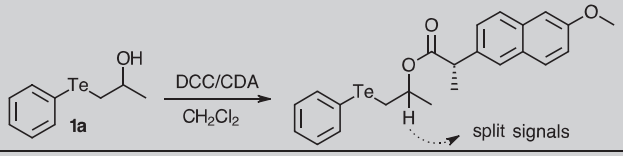
Entry	Chalcogen Alcohol	Solvent	$\Delta\delta$, ppm	$\Delta\delta$, Hz
1	**1a**	$CDCl_3$	0.0064	3.2
2	**1a**	C_6D_6	0.0069	3.5
3	**1b**	$CDCl_3$	0.0046	2.3
4	**1b**	C_6D_6	0.0071	3.6
5	**1c**	C_6D_6	0.0064	3.2
6	**1d**	C_6D_6	0.0045	2.3
7	**1d**	$CDCl_3$	---[c]	---[c]

[a]1.0 equiv. of alcohol **1** with 1.0 equiv. of (+)-BINOL and 1.0 equiv. of DMAP in the deuterated solvent (20 mM).

[b]Excess of DMAP (2.0 or 3.0 equiv.) did not demonstrate improvements.

[c]There was no $\Delta\delta^{RS}$ value.

TABLE 2 ^{1}H and ^{125}Te-$\{^{1}H\}$ NMR chiral discrimination of tellurium containing secondary alcohol **1a** by CDAs[a,b]

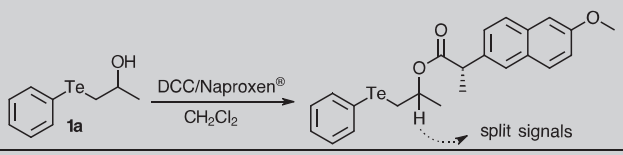


Entry	CDA	NMR Exp.	$\Delta\delta$, ppm	$\Delta\delta$, Hz
1	(+)-Mand. acid	^{125}Te-$\{^{1}H\}$	---	---
2	(+)-Mand. acid	^{1}H	---	---
3	(+)-MTPA	^{125}Te-$\{^{1}H\}$	---	---
4	(+)-MTPA	^{1}H	---	---
5	(+)-Naproxen	^{125}Te-$\{^{1}H\}$	1.10	104.0
6	(+)-Naproxen	^{1}H	0.54	164.6

[a]1.0 equiv. of alcohol **1a** with 1.0 equiv. CDA and 1.0 equiv. of DCC in 2 mL of CH_2Cl_2 solvent at 30 °C.

[b]The (+)-Naproxen ester was purified by column chromatography and analysed by ^{1}H (300 MHz) and ^{125}Te-$\{^{1}H\}$ (94.7 MHz) NMR.

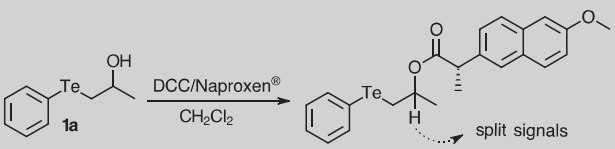
TABLE 3 Evaluation of the deuterated solvent in the ^{1}H and ^{125}Te-$\{^{1}H\}$ NMR chiral discrimination of tellurium containing secondary alcohol **1a** by Naproxen drug as a CDA[a,b]



Entry	Solvent	NMR Exp.	$\Delta\delta$, ppm	$\Delta\delta$, Hz
1	C_6D_6	^{125}Te-$\{^{1}H\}$	1.63	154.0
2	C_6D_6	^{1}H	0.035	10.4

(Continues)

TABLE 3 (Continued)



Entry	Solvent	NMR Exp.	Δδ, ppm	Δδ, Hz
3	Py-d_5	^{125}Te-{^{1}H}	0.89	84.2
4	Py-d_5	^{1}H	---[c]	---[c]

[a]The samples were prepared by weighing and dissolving the appropriate amount of Naproxen ester derived from alcohol **1a** to obtain a 20 mM solution.

[b]The (+)-Naproxen ester was purified by column chromatography and analysed by ^{1}H (300 MHz) and ^{125}Te-{^{1}H} (94.7 MHz) NMR.

[c]There was no $\Delta\delta^{RS}$ value.

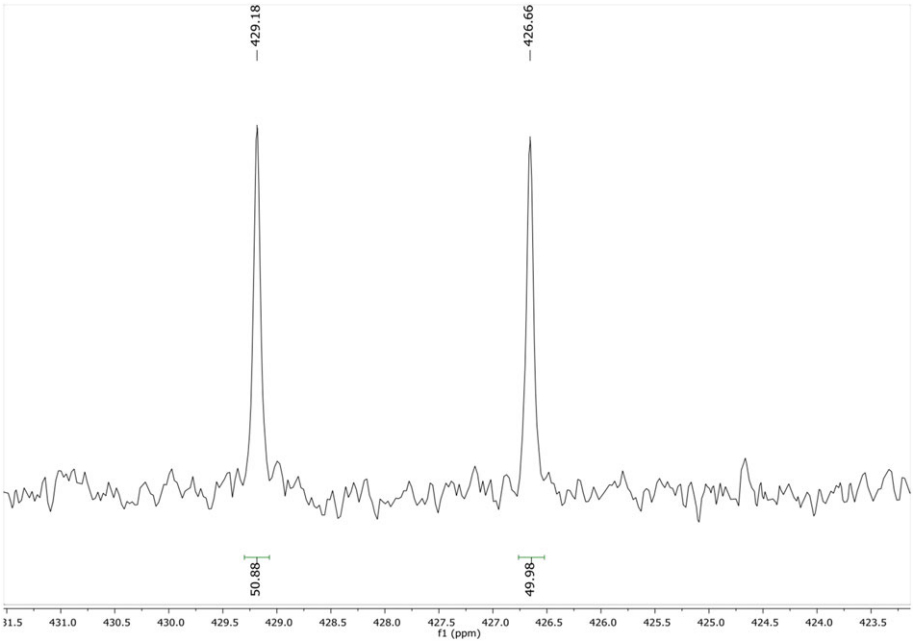
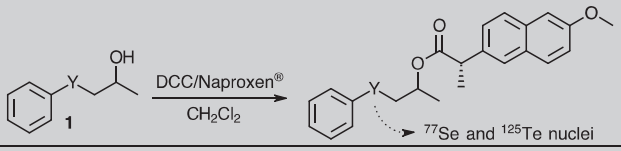


FIGURE 1 ^{125}Te-{^{1}H} (94.7 MHz) NMR spectrum of Naproxen ester derived from tellurium containing secondary alcohol **1h** in $CDCl_3$ at 298 K

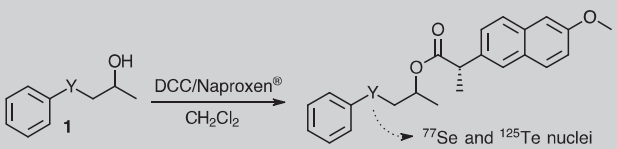
TABLE 4 ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} NMR chiral discrimination of chalcogen containing secondary alcohol **1** by Naproxen as a CDA[a,b]



Entry	Chalcogen Alcohol 1	NMR Exp.	Δδ, ppm	Δδ, Hz
1	**1a**	^{125}Te-{^{1}H}	1.10	104.0
2	**1b**	^{77}Se-{^{1}H}	1.37	78.4
3	**1c**	^{77}Se-{^{1}H}	---[c]	---[c]
4	**1d**	^{125}Te-{^{1}H}	---[c]	---[c]
5	**1e**	^{77}Se-{^{1}H}	1.47	84.1
6	**1f**	^{125}Te-{^{1}H}	0.60	56.8

(Continues)

TABLE 4 (Continued)



Entry	Chalcogen Alcohol 1	NMR Exp.	$\Delta\delta$, ppm	$\Delta\delta$, Hz
7	**1g**	^{125}Te-{^{1}H}	0.76	72.3
8	**1h**	^{125}Te-{^{1}H}	2.52	239.5
9	**1i**	^{77}Se-{^{1}H}	0.27	15.4
10	**1j**	^{125}Te-{^{1}H}	0.04	3.3
11	**1 k**	^{77}Se-{^{1}H}	1.73	99.3

[a]1.0 equiv. of alcohol **1** with 1.0 equiv. Naproxen and 1.0 equiv. of DCC in 2 mL of CH_2Cl_2 solvent at 30 °C.

[b]The (+)-Naproxen esters were purified by column chromatography and analysed by ^{77}Se-{^{1}H} (57.4 MHz) and ^{125}Te-{^{1}H} (94.7 MHz) NMR.

[c]There was no $\Delta\delta^{RS}$ value.

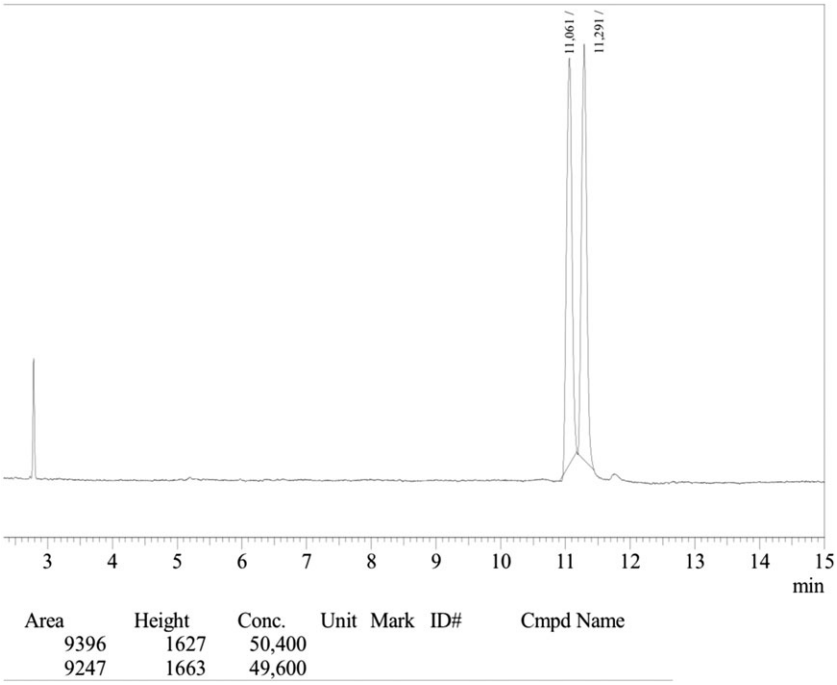
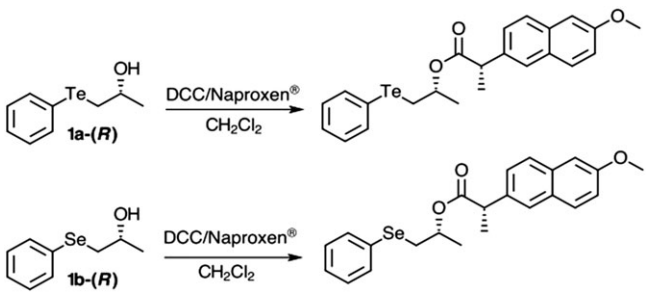


FIGURE 2 Enantiomer ratio evaluation of tellurium containing secondary alcohol **1a** by chiral chromatographic gas analysis



SCHEME 2 Synthesis of enantiopure Naproxen esters derived from (*S*)-Naproxen and (*R*)-chalcogen containing secondary alcohols **1a** and **1b**

$\Delta\delta^{RS}$ value of the CH_3 group in deuterated benzene of the ^{1}H NMR increased. This type of result is difficult to predict and is caused by the anisotropic effect of the solvent.[21] When deuterated pyridine was employed, the split signal decreased for the ^{125}Te-{^{1}H} NMR spectrum and vanished for the ^{1}H NMR spectrum (Table 3, entries 3 and 4).

These results exalt the advantages of multinuclear NMR spectroscopy because of the substantial $\Delta\delta^{RS}$ values and no overlapping of the signals. ^{77}Se and ^{125}Te NMR have great potential due to the characteristics of selenium and tellurium nuclei, such as a wide spectral window,

FIGURE 3 ^{77}Se-{^{1}H} (54.7 MHz), and ^{125}Te-{^{1}H} (94.7 MHz) NMR spectra of Naproxen esters derived from (*S*)-Naproxen and the racemic or (*R*)-enantiomer chalcogen containing secondary alcohols **1a** and **1b**. ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} NMR spectra were recorded in $CDCl_3$ at 298 K

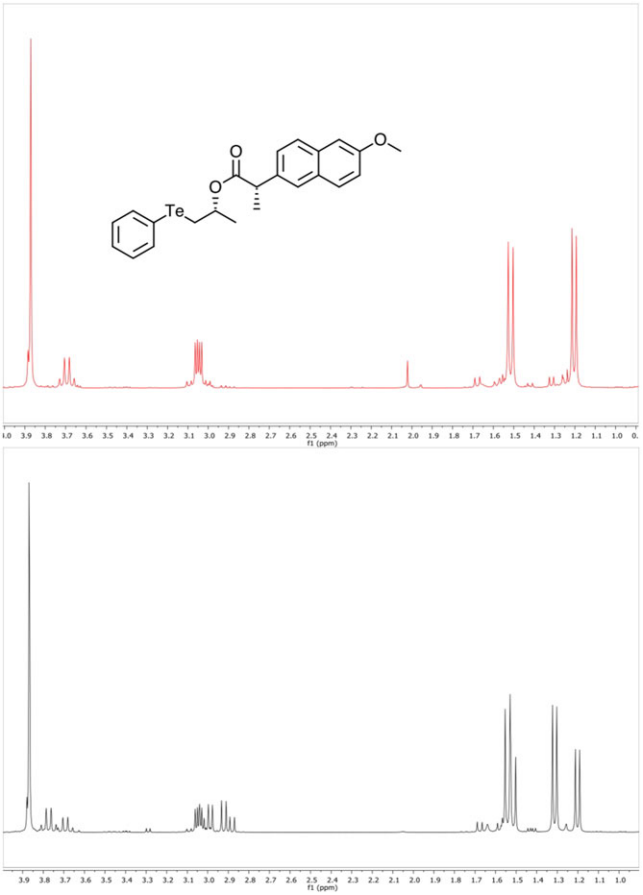


FIGURE 4 ^{1}H (300 MHz) NMR spectra of (*S*)-Naproxen esters derived from the racemic (bottom spectrum) and (*R*) (up spectrum) enantiomer of tellurium containing secondary alcohol **1a** in $CDCl_3$ at 298 K

$I = ½$, reasonably high natural abundance, and no significant nuclear Overhauser effect (nOe).[22] These great features can be witnessed by observing the ^{125}Te-{^{1}H} NMR spectra of Naproxen ester formed from chalcogen containing secondary alcohol **1h** (Figure 1).

Furthermore, multinuclear NMR spectroscopy is an efficient alternative to overcome ^{1}H NMR limitations,[23] such as overlap of signals, combined with broad and featureless spectra. Therefore, the ^{1}H NMR spectra of Naproxen ester derived from chalcogen containing secondary alcohol **1a** is severely hampered due to the numerous scalar couplings.

With the possibility of performing the reaction inside the NMR tube without purification, the mix and shake

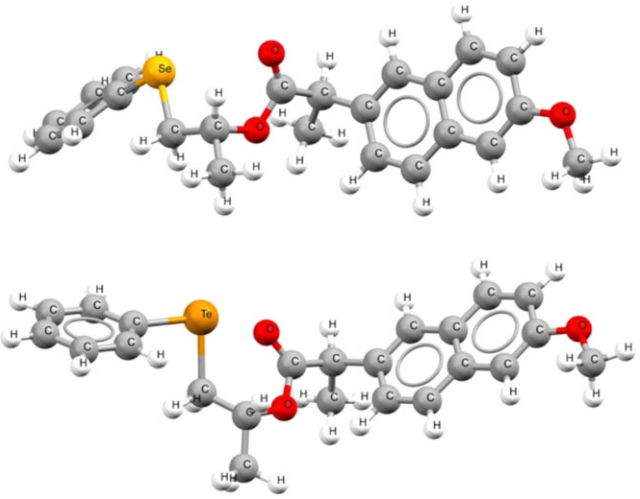
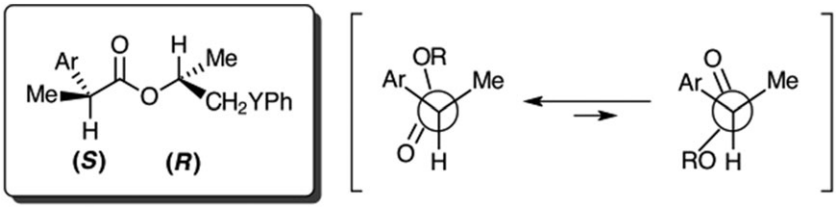


FIGURE 5 Calculated conformational structures of Naproxen esters derived from chalcogen containing secondary alcohols **1a** and **1b** using PM6 semiempirical method

method was tested. For this purpose, chalcogen alcohol **1a** (0.05 mmol), Naproxen (0.05 mmol), and DCC (0.05 mmol) were added in a 5-mm NMR tube with 600 μL of $CDCl_3$. Shaking was carried out for 2 minutes. After this time, the NMR tube showed the presence of a white solid in suspension. After 30 minutes, the white solid was decanted. Then, the ^{125}Te-{^{1}H} NMR experiment was possible. By using the DIC as a coupling reagent, there was no white solid and the ^{125}Te-{^{1}H} NMR experiment was recorded immediately. Chalcogen alcohol **1a** and the intermediate of the coupling reaction were observed by ^{1}H NMR spectra in the mix and shake protocol using the DIC coupling reagent.

Finally, with the best conditions established, we expanded the mix and shake methodology ((*S*)-Naproxen/DCC) for other secondary chalcogen alcohol **1**. As can be seen in Table 4, the $\Delta\delta^{RS}$ values of ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} NMR spectra were superior than the ^{1}H NMR experiments, and there was no overlapping of signals. In most cases, selenium and tellurium nuclei demonstrated the same profile of anisotropy diamagnetic and, consequently, a similar $\Delta\delta^{RS}$ values. For chalcogen alcohol **1h**, the $\Delta\delta^{RS}$ value was higher than other chalcogen alcohols (Table 4, entry 6). There was no splitting of the signals in chalcogen alcohols **1c** and **1d**. The presence of the butyl group in the chalcogen atom disturbed the



SCHEME 3 Effect of the shielding cone by carbonyl on the C_α-H organic groups in the esters derived from (*S*)-Naproxen and (*R*)-chalcogen containing secondary alcohols **1a** and **1b**

anisotropic effect. The results reveal that the group bonded to the chalcogen atom is important for the effectivity of ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} NMR chiral discrimination. The presence of an aryl ring can afford significant shielding and upfield shifts of the resonances of the alcohol hydrogen and chalcogen atoms that are positioned closer to the ring.

In some chalcogen alcohol **1**, the derivatization with Naproxen drug was followed by overlapping of the signals in the ^{1}H NMR experiments. Otherwise, there were exceptions, as chalcogen alcohol **1j** had a $\Delta\delta^{RS}$ value of Naproxen ester that was 0.11 ppm (33.7 Hz). There was also splitting of the methoxyl signals from the Naproxen group (Figure S41, $\Delta\delta^{RS}$ = 0.012 ppm). Moreover, the ^{125}Te-{^{1}H} NMR chiral discrimination of chalcogen alcohol **1j** was less efficient (Table 4, entry 10). This outcome established a connection between the efficacy of proton and chalcogen nuclei in the NMR chiral discrimination, possibly due to the conformational structures involved in the anisotropic effect.

A significant difference in the signal integration of the ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} NMR spectra of the Naproxen ester derivatives formed from chalcogen containing secondary alcohols **1a**, **1b,** and **1k** was detected (Figure S42, 62:38 ratio, instead of 50:50 ratio). These results were a consequence of the kinetic resolution of the enantiomers during the Naproxen coupling reaction and were confirmed by chiral chromatographic gas analysis (Figure 2). The ^{1}H NMR chiral discrimination of the respective chalcogen containing secondary alcohols using the ternary chiral complex ((+)-BINOL/DMAP) methodology combined with the deconvolution procedure did not show kinetic resolution of the enantiomers (Figure S55). Thus, for the enantiomeric excess (*ee*) measurement, the ternary complex system can be used employing ^{1}H NMR spectroscopy in a simple and rapid method. Although, in some chalcogen containing secondary alcohol **1** evaluated (chalcogen containing alcohols **1e**, **1f**, **1g**, **1h**, **1i**, and **1j**), Naproxen/DCC was an effective protocol without the enantiomer kinetic resolution (Support Information).

3.3 | Assignment of the absolute configuration

Another evaluation to carry out was the assignment of the absolute configuration of the chalcogen containing secondary alcohol **1**. To obtain the enantiopure chalcogen containing secondary alcohols **1a** and **1b**, the ring-opening reaction between (*R*)-(+)-propylene oxide and the anion phenylchalcogenolate was performed. After, the derivatization of enantiopure chalcogen containing secondary alcohols **1a** and **1b** were performed using the protocol DCC/(*S*)-(+)-Naproxen in CH_2Cl_2 (Scheme 2).

With the Naproxen esters containing the chalcogen atoms in hand, ^{1}H, ^{77}Se-{^{1}H}, and ^{125}Te-{^{1}H} NMR experiments were recorded. As can be seen in Figure 3, ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} chemical shifts do not have the same pattern. In the ^{77}Se-{^{1}H} NMR of the Naproxen ester of (*S*)-Naproxen and (*R*)-selenide alcohol **1b**, the chemical shift was downfield, and for the ^{125}Te-{^{1}H} NMR of the Naproxen ester of the (*S*)-Naproxen and (*R*)-telluride alcohol **1a**, the chemical shift was upfield. According to the ^{1}H NMR spectra, the proton chemical shifts of enantiopure Naproxen esters of chalcogen alcohols **1a** and **1b** demonstrated the same profile. These results confirm the major precision of ^{1}H NMR spectroscopy in the assignment of absolute configuration.

To understand the conformation of the chiral structures, the ^{1}H NMR spectra were analysed. As can be seen in Figure 4, the CH_3 and CH groups of the alcohol substrate are shielded. The opposite was observed for CH_2. The CH_3 group of the Naproxen substrate was shielded in the ^{1}H NMR spectra. Based on the Mosher model, the shielding effect of both CH_3 groups is due to the spatial orientation of the Naproxen ester of (*S*)-Naproxen and (*R*)-chalcogen alcohol, which are the CH_3 groups suffering the anisotropic effect of the aromatic rings (Scheme 3). Shielding of the CH group can be visualized by the conformational preference of the Naproxen ester. The CH group is shielded by the cone of the carbonyl group (Scheme 3). These results are in agreement with the assignment of the absolute configuration of aminophosphonates by Naproxen.[10]

An estimate of chalcogen chemical shifts for chiral Naproxen ester derivatives **1a** and **1b** may be provided by semiempirical method. Thus, the molecular geometry of the compounds was optimized using the PM6 and PM7 methodologies.[24,25] To understand the ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} chemical shifts and provide additional insight into chalcogen organic compounds, the molecular structure of both chiral compounds is presented (Figure 5). Firstly, the shielding of the CH group can be confirmed by the torsion angle with the carbonyl group (11° for **1b** and 13° for **1a**). This geometry shows the proximity between the chalcogen elements with the oxygen atom from carbonyl group (Se-O is 3.496 Å and Te-O is 2.181 Å). These distances could be explained by electrostatic sigma-hole interactions.[26] Chalcogen bonding (ChB) plays as a conformational lock to stabilize the interaction between nearby heteroatoms (O and N) with low-valent heavy chalcogen by charge transfer to the antibonding orbital. Based on the molecular geometries (Figure 5), the shortest distance of tellurium element represents a greater sigma-hole interaction. The ^{125}Te-{^{1}H}

chemical shift in the chiral Naproxen ester **1a** was shielded by the cone of the carbonyl group. The ^{77}Se-{^{1}H} chemical shift in the chiral Naproxen ester **1b** is not affected by this shielding, and is in agreement with the ^{1}H NMR chemical shifts.

4 | CONCLUSION

In this work, general strategies were evaluated to explore the NMR chiral discrimination of chalcogen (Se and Te) containing secondary alcohols. The (+)-BINOL/DMAP ternary complex demonstrated a rapid and simple procedure to evaluate the enantiopurity of the chalcogen alcohols. (*S*)-Naproxen was an effective chiral derivatizing agent. Moreover, (*S*)-Naproxen is a stable, nonhygroscopic, and readily available compound. ^{77}Se-{^{1}H} and ^{125}Te-{^{1}H} NMR spectroscopy were useful to overcome limitations such as smaller $\Delta\delta^{RS}$ values and overcrowded ^{1}H NMR spectra. The assignment of absolute configuration was performed by ^{1}H NMR spectroscopy. The conformation of the (*S*)-Naproxen esters were similar to the literature, providing confidence for using this CDA for other related structures.

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ORCID

Eder J. Lenardão http://orcid.org/0000-0001-7920-3289
Márcio S. Silva http://orcid.org/0000-0002-7606-564X

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