Using ^{1}H NMR and Chiral Chemical Shift Reagent to Study Intramolecular Racemization of Pentacyclo Pure Enantiomer by Thermal Dyotropic Reaction

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Abstract: *In this work, we describe the use of ^{1}H NMR using a chiral chemical shift reagent as an alternative method to gas chromatography on a chiral column to determine the enantiomeric excess of the enantiomer (+)-10-exo-hydroxy-pentacyclo [6.2.1.1^{3,6}.0^{2,7}.0^{5,9}] dodeca-4-one* ***(+)-1*** *and the thermal dyotropic racemization process, which occurs when compound* ***(+)-1*** *is submitted to chiral gas chromatography analysis.*

Resumo: *Neste trabalho, descreve-se o uso de RMN de Hidrogênio utilizando-se reagente de deslocamento químico quiral, como um método alternativo à cromatografia gasosa em coluna quiral, para determinar o excesso enantiomérico do enantiomero (+)-10-exo-hidroxi-pentaciclo [6.2.1.1^{3,6}.0^{2,7}.0^{5,9}] dodeca-4-one* ***(+)-1****, assim como a sua racemização através de um processo térmico diotrópico quando o mesmo é analisado por cromatografia gasosa em coluna quiral.*

Introduction

In the last years, our group has been interested in the spectroscopic aspects of polycyclic compounds such as bicyclic, tricyclic, tetracyclic, pentacyclic and hexacyclic derivatives.[1] The kinetic resolution of polycyclic compounds has been one of our recent focus with the aim to obtain enantiopure alcohols.[2] Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy with a chiral chemical shift reagent is an alternative method to determine the enantiomeric excess of chiral compounds when other methods like gas chromatography (GC) using a chiral column fail.[1b, c]

Herein, we describe the use of a chiral chemical shift reagent as an alternative method to GC on a chiral column. The aim is to determine the racemization of pentacyclic alcohol **(+)-1** by intramolecular thermal dyotropic reaction as well as its enantiomeric excess.

Experimental

NMR spectra were measured with a VARIAN VXR200 (B_0 = 4.7 T) and YH-300 (B_0 = 7.05 T). Chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and the *J* values are given in Hz. The chromatograms were obtained using a Shimadzu GC-17A Gas Chromatograph equipped with a FID detector. The parameters used for chiral analysis were as follows: Injector 250 ^{0}C; detector 300 ^{0}C; oven 170 ^{0}C for 15 min then 1 ^{0}C/min until 200 ^{0}C;column pressure 100 kPa; column flow 33 mL/min; split ratio 1:10. Column β-Dex 120 chiral GC column (30m x 0.25 mm). Optical rotations were measured in a Perkin-Elmer 341 polarimeter with a 0.1 dm cell at a temperature of 20^{o}C.

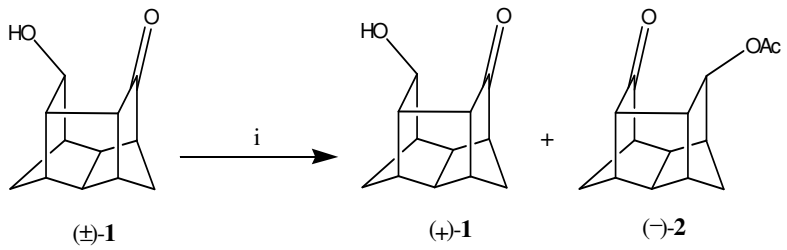
Enantiomeric excess analysis by ^{1}H NMR spectroscopy using the chiral chemical shift reagent

High resolution of signals has been achieved for the enantiomeric proton H(10) (α-OAC) of (±)-**2**. Sequential addition of the chiral chemical

shift reagent tris [3-(heptafluoropropylhydroxymethylene) - (+) - camphorate] europium (III) [1b,c] $Eu(hfc)_3$ (5 mg) to a $CDCl_3$ solution of (±)-**2** (10 mg) in a 5 mm NMR tube, provided the best result with 25 mg of $Eu(hfc)_3$. The difference in chemical shift ($\Delta\Delta\delta$) of enantiomeric hydrogen H(10) (α-OAc) was 0.16 ppm.

Results and Discussion

In order to obtain the enantiopure form of pentacyclic **1**, the racemic mixture **(±)-1** was transesterified with vinyl acetate catalyzed by lipase from Candida *rugosa*, giving the acetylated compound (–)-**2** and remaining alcohol **(+)-1** (Scheme **1**).[3]



(i) Vynyl acetate, Lipase from *Candida rugosa,5 hours,* 46 % of convertion

Scheme 1. Kinetic resolution of **(±)-1**

After five hours with a chemical conversion of 46 %, the products were separated by silica gel column. Firstly we analyzed the enantiomeric excesses of the products by GC in a chiral column, but this technique did not allow good separation of signals for the racemic standard **(±)-2**, although we have tried it with different methods and columns. However, for the racemic standard **(±)-1** good separation of signals was possible using such a technique. Figure **1** shows the analysis of the reaction mixture of the kinetic resolution of **(±)-1** by GC on a chiral column. Figure **1** shows a unique signal at 31.4 minutes relative to ester **(–)-2** and two signals at a 1:1 ratio relative to alcohol **(+)-1**, possibly indicating racemization.

As separation of enantiomeric signals of standard **(±)-2** using GC was not effective, the enantiomeric excess analysis of **(–)-2** was performed by ^1H NMR using the chiral chemical shift reagent tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] europium (III) ($Eu(hfc)_3$). This analysis presented high resolution of signals for the enantiomeric protons H (10) (α-OAc) of the standard **(±)-2** (Figure **2**).

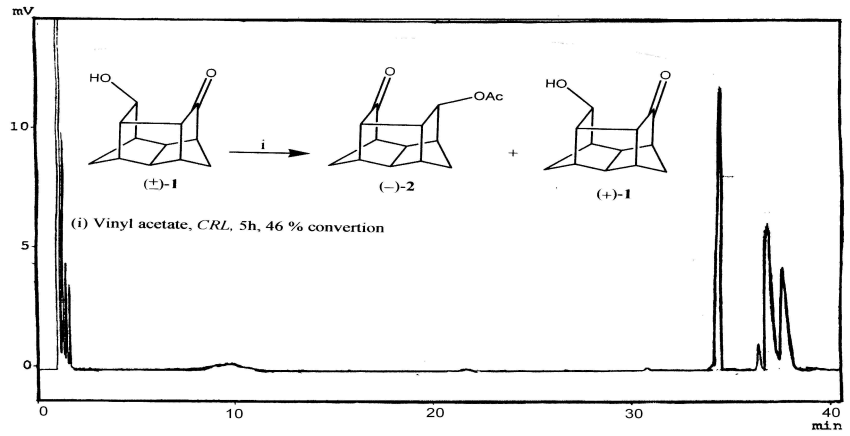


Figure 1. Chromatogram of the reaction mixture

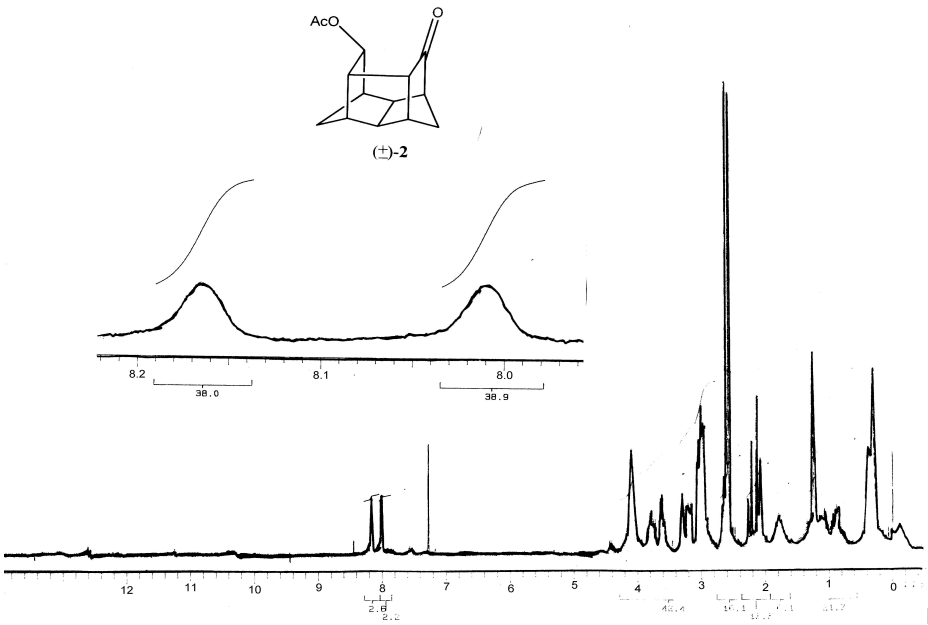


Figure 2. ^{1}H NMR spectrum of **(±)-2** with 20 mg of Eu (hfc)$_3$.

Figure **3** shows the enantiomeric excess analysis of chiral ester **(–)-2** by ^{1}H NMR using the chiral chemical shift reagent. This analysis showed enantiomeric excess up to 95 % for the keto-acetate (–)-**2**. However, the GC analysis of **(+)-1** using a chiral column showed the two enantiomeric signals at a ratio of 1:1, corresponding to the racemate **(±)-1** (Scheme **2** and Figure **4**).

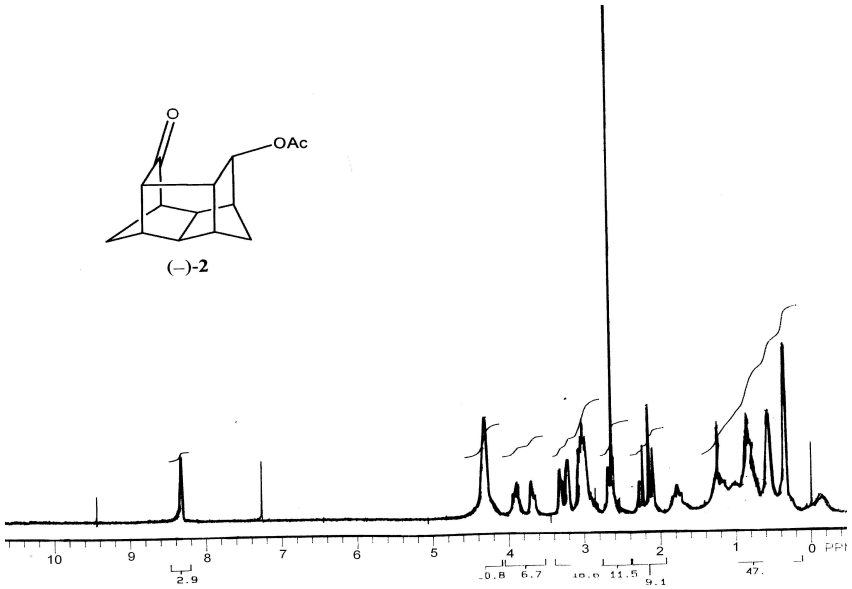
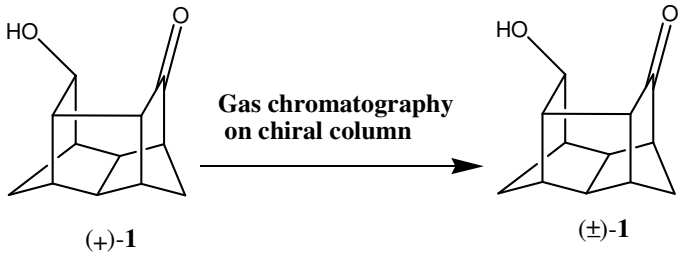


Figure 3. 1H NMR spectrum of **(–)-2** with 20 mg of $Eu(hfc)_3$



Scheme 2. Racemization of **(+)-1**

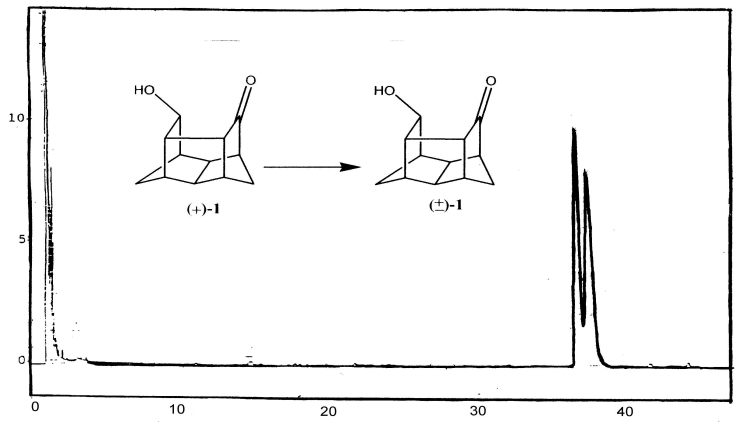
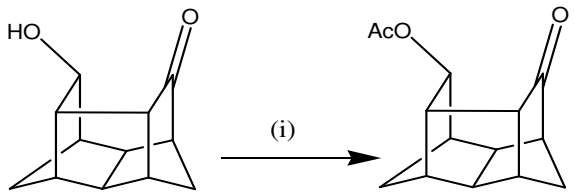


Figure 4. Chiral GC analysis showing racemization of **(+)-1**

This result was somewhat unexpected, and we thus performed the enantiomeric excess analysis of **(+)-1** using ^{1}H NMR with a chiral chemical shift reagent. However, the standard **(±)-1** did not present a satisfactory separation of enantiomeric signals. We then determined the enantiomeric excess of **(+)-1** by preparing its acetylated derivative through the reaction of **(+)-1** with acetic anhydride (Scheme **3**). The acetylated compound **(+)-2** was then analyzed by ^{1}H NMR under the same conditions employed for **(–)-2**, showing an enantiomeric excess of 85% (Figure **5**).



(+)-**1** (+)-**2**

(i) acetic anhydride, DMAP, CH_2Cl_2, r. t

Scheme 3. Acetylation of **(+)-1**

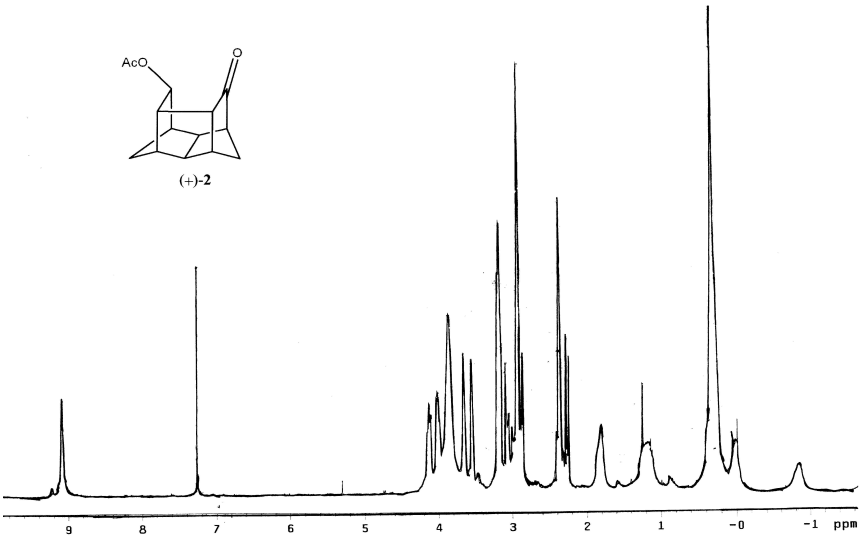
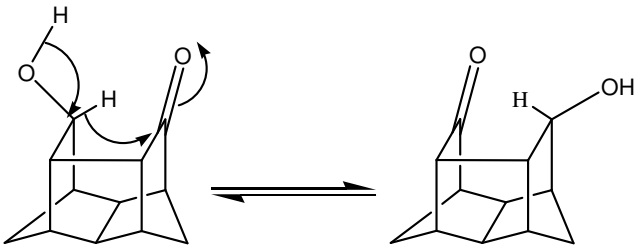


Figure 5. 1H NMR spectrum of **(+)-2** with 20 mg of $Eu(hfc)_3$

The result of the analysis of **(+)-1** by chiral GC (Figure **4**), when racemization occurred, could be explained by a dyotropic intramolecular rearrangement producing the correspondent racemate (Scheme **4**).



(+)-**1** (−)-**1**

Scheme 4. Racemization process of **(+)-1**

This data suggests that the high temperature used in GC analysis can promote this dyotropic rearrangement. To confirm this hypothesis, we heated the compound **(+)-1** at 170 ^{0}C in a vacuum-sealed ampoule, and we observed the same dyotropic intramolecular rearrangement.

Conclusion

It is impossible to determine the enantiomeric excess of **(+)-1** by GC analysis on a chiral column, due to thermal racemization by a dyotropic process resulting from orbital symmetry. ^{1}H NMR, using the chiral chemical shift reagent, (Eu (hfc)$_3$), has shown to be an excellent alternative method to overcome this problem. This method showed an enantiomeric excess >95% for **(-)-2** and 85% for **(+)-1**.

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