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## Practical access to (S)- heterocyclic aromatic acetates via CAL-B /Na<sub>2</sub>CO<sub>3</sub>-deacylation and Mitsunobu reaction protocol

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Nabila Braïa, Mounia Merabet-Khelassi, Martial Toffano, Louisa Aribi-Zouioueche. Practical access to (S)- heterocyclic aromatic acetates via CAL-B /Na<sub>2</sub>CO<sub>3</sub>-deacylation and Mitsunobu reaction protocol. *Biocatalysis and Biotransformation*, 2022, pp.1-9. 10.1080/10242422.2022.2030726 . hal-03578388

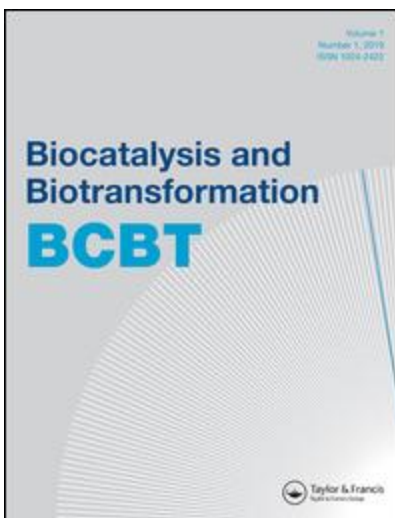
**HAL Id: hal-03578388**

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Submitted on 17 Feb 2022

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**Practical access to (S)-heterocyclic aromatic acetates via  
CAL-B/Na<sub>2</sub>CO<sub>3</sub>-deacylation and Mitsunobu reaction  
Protocol.**

Journal:	<i>Biocatalysis and Biotransformation</i>
Manuscript ID	Draft
Manuscript Type:	Original Paper
Date Submitted by the Author:	n/a
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Keywords:	Heteroaromatic carbinol, Enzymatic kinetic resolution, Hydrolysis, CAL-B, Na <sub>2</sub> CO <sub>3</sub> , Deracemization

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**Abstract:**

Herein, we report for the first time the preparation of enantiomerically pure forms of 2,3-dihydrobenzofuran-3-ol (**1**), chroman-4-ol (**2**), thiochroman-4-ol (**3**), 1-(furan-2-yl) ethanol (**5**) and 1-(thiophen-2-yl) ethanol (**6**), using kinetic resolution *via* *CAL-B* / Na<sub>2</sub>CO<sub>3</sub> hydrolysis in organic media. The (*R*)-furnished alcohols and the (*S*)-remained acetates are recovered enantiopures (ee>99%, E>>200, Conv=50%). Those ideal EKR are well incorporated to the Mitsunobu inversion protocol in a one pot procedure to give (*S*)-heterocyclic acetates (**1a-3a**) in good to excellent enantiomeric excess 88%<ee<92%. Whilst, the (*S*)-heteroaromatic acetates (**5a-6a**) are given in moderate enantiomeric excess 51%<ee<62%. All the (*S*)-acetates are given in good isolated chemical yields (>80%) allowing to overcome the maximum of 50% yield which could be usually reached in a regular KR-processes. To date, the enzymatic resolution of 2,3-dihydrobenzofuran-3-ol (**1**) and their acetate is rarely described.

**Keywords:**

Heterocyclic carbinols, Heteroaromatic carbinol, Enzymatic kinetic resolution, Hydrolysis, *CAL-B*, Na<sub>2</sub>CO<sub>3</sub>, Mitsunobu esterification, Deracemization *via* stereoinversion.

## 1. Introduction

Heterocyclic and heteroaromatic carbinols containing oxygen or sulfur are important cores found in many biologically natural products, or used as a key chiral synthons to obtain a large number of complex bioactive molecules used in pharmaceutical, flavor and fragrance industries (Andersen et al. 2006; Veitch and Grayer 2011). Moreover, oxygen heterocycles are the second most common type that appears as structural components of U.S. Food and Drug Administration (FDA) approved pharmaceuticals (Delost et al. 2018). Chroman-, thiochroman, furyl- and thiofuryl- carbinol derivatives present an anti-inflammatory, anti-bacterial, anti-oxidant, anti-carcinogenic as well as  $\beta$ -blockers activities (Debayan et al. 2017; Wallert et al. 2020) or anti-oxidative properties, like molecules of the vitamin E family who exert anti-atherogenic and anti-inflammatory activities (El Hadi et al. 2018; Nagashimada and Tsuguhito 2019). 2,3-dihydrobenzofuran-3-ols (coumarane) skeletons are also present in high valuable bioactive molecules (Bertolini and Pineschi 2009; Ni et al. 2020) (Figure 1).

**Figure 1:** Some bioactive molecules within heterocyclic (aromatic) fragment.

Hence, the need of development of green and sustainable methods for the preparation of a single enantiomerically pure form of those active pharmaceutical ingredients (APIs) stills an important synthetic challenge.

Enzymatic kinetic resolution is the most efficient methods allowing smoothly preparing enantiopure pharma intermediates (Dunn 2012; Sheldon et al. 2020; Wu et al. 2021), especially since biocatalytic processes perfectly integrate with a majority of the principles of green chemistry (Sheldon et al. 2011). Among used enzymes, lipases (triacylglycerol acyl hydrolases, EC.3.1.1.3) have paid growing attention for their technical and environmental advantages: ease of use under mild conditions, recyclability, and biodegradability, without the use of cofactors, excellent stability in organic solvents and for their remarkable *chemo*-, *regio*- and *enantio*-selectivity. The lipase from *Candida antarctica* fraction B, under an immobilized form, is one of the most useful due to their exclusive properties such as facile recovery, thermostability, environmental benign (Idris and Attaullah 2012). This methodology can be carried out by transesterification in organic solvents or hydrolysis in water, albeit with the main drawback of a poor atom economy, as the maximum theoretical yield of 50% (Faber 2011). To circumvent this limitation several deracemization methods have been developed and have led access to single enantiomer with high optical purity and good chemical yields (Turner 2010; Musa et al. 2019; Aranda et al. 2020).

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5 The preparation of enantiomerically pure forms of heterocyclic and heteroaromatic carbinols  
6 using kinetic resolution *via* enzymatic acylation is scarcely reported (Olexandr et al. 2014;  
7 Ferrerira et al. 2016) and that of hydrolysis was used even less (Kang et al. 1995; Holmberg  
8 et al. 2005). Furthermore, at the best of our knowledge the enzymatic kinetic resolution of  
9 2,3-dihydrobenzofuran-3-ol and their acetate is rarely described (Honig et al. 1994).  
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14 In the present paper, we describe for the first time the kinetic resolution of few heterocyclic  
15 and heteroaromatic carbinols *via* enzymatic-alkaline hydrolysis, a simple and practical  
16 enzymatic hydrolysis method developed in our laboratory, with sodium carbonate in organic  
17 medium catalyzed by *CAL-B* lipase (Merabet-Khelassi et al. 2012). This approach has been  
18 used effectively on many substrates such as arylalkylcarbinol acetates (Houiene et al. 2013),  
19 *N,O*-protected amino alcohols (Alalla et al. 2016), 2-aryl-1-cyclohexyl acetates (Belkacemi et  
20 al. 2017) and 3-(1-hydroxyethyl)phenol (Braia et al. 2018). This reaction has been integrated  
21 to the heterocyclic aromatic alcohols and incorporated to a deracemization process *via*  
22 stereoinversion (Bouzemi et al. 2006; Houiene et al. 2013) with the Mitsunobu esterification  
23 (Mitsunobu and Yamada 1967) to gave quantitatively access to the (*S*)-heterocyclic  
24 (aromatic) acetates. (Scheme 1)  
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### Scheme 1: Our present investigation

## 2. Materials and methods:

### 2.1. Chemicals and Materials

All reagents purchased from: Aldrich, were used as received. The *Candida Antarctica lipase* immobilized on acrylic resin *CAL-B* was purchased from Aldrich. Specific activity >5 000U/g used without any pre-treatment. Reactions were monitored by thin-layer chromatography (TLC) carried out on Silica gel 60F<sub>254</sub> plates type *MERCK* 5179, 250 mesh, using UV light (254 nm) as the visualizing agent. The separation of the resulting alcohols and the remaining acetates was performed by column chromatography using Silica gel 60Å, 70-230 mesh 63-200µm.

### 2.2. Instrumentations

NMR spectra were recorded on Bruker spectrometers (300 MHz for <sup>1</sup>H, 75 MHz for <sup>13</sup>C) instrument and calibrated using residual deuterated solvent as an internal reference (peak at

7.26 ppm in  $^1\text{H}$  NMR and 3 peaks at 77 ppm in  $^{13}\text{C}$  NMR in the case of  $\text{CDCl}_3$  and DMSO. The following abbreviations were used to designate multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br: broad signal, dd=double-doublet. Chemical shifts were expressed in ppm and coupling constant ( $J$ ) in Hz. The enantiomeric excesses were measured by a chiral stationary phase HPLC: *Chiralpak* OD-H column (4.6 × 250 mm), *Chiralpak IA* column (4.6 × 250 mm). Retention times are reported in minutes. Optical rotations were determined using a Perkin-Elmer 341 Polarimeter at room temperature using a cell of 1 dm length and  $\lambda = 589$  nm.

### 2.3. General procedures of all racemic compounds:

#### 2.3.1. Synthesis of racemic alcohols (1-6):

All racemic alcohols (1-6) were prepared from the corresponding commercial ketones using the following procedure: to solution of THF /  $\text{H}_2\text{O}$  (4/1, v/v), 6 equivalent of sodium borohydride (18 mmol) are added, and stirred at  $0^\circ\text{C}$ . 3 mmoles of the corresponding alcohol diluted in 20mL of THF are added by drops. After consumption the ketone, the mixture was neutralized by addition of a solution of (HCl, 1N). Then the organic layer was removed, and the aqueous layer was extracted with ethyl acetate (3 x 80mL). The combined organic layers were dried over anhydrous  $\text{MgSO}_4$  and concentrated to give the corresponding alcohols with good yields. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of these products were in good agreement with the literature.

**2,3-Dihydro-benzofuran-3-ol (1):**  $\text{C}_8\text{H}_8\text{O}_2$  Crude oil. Yield = 72%.  $R_f = 0.15$ . Eluent (v,v): petroleum ether /ethyl acetate (80/20).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.3 (s, 1H, OH); 4.43 (ddd,  $J = 13.4, 10.7, 4.5$  Hz, 2H); 5.28 (dd,  $J = 6.4, 2.6$  Hz, 1H); 6.92 (ddd,  $J = 14.5, 10.6, 4.5$  Hz, 2H); 7.33 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 72.1, 79, 110.54, 121, 125.4, 175.4, 128.2, 130.7.

**Chiral HPLC:** *Chiralpak IA* column,  $t_R = 16.85$  min,  $t_S = 18.46$  min. Eluent (v,v): *n*-hexane/ iPrOH: 95/5; flow rate: 0.7 mL/min .

**Chroman-4-ol (2):**  $\text{C}_9\text{H}_{10}\text{O}_2$  Uncolored oil. Yield = 90%.  $R_f = 0.17$ . Eluent (v,v): petroleum ether /ethyl acetate (80/20).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  : 2 (m,2H) 2.15 ( br s, 1H); 4,3 (m, 2H) ; 4,8 (t, 1H,  $J = 4$  Hz ) ; 6.96 (m, 2H), 7.19–7.5 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 30.8; 61.9; 63.1; 117; 120.5; 124.3; 129.6; 129.7; 154.5.

**Chiral HPLC:** *Chiralpak ODH* column,  $t_S = 19.73$  min,  $t_R = 23.00$  min. Eluent (v,v): *n*-hexane/iPrOH: 95/5; flow rate: 0.5mL/min.

**2,3-dihydrothiochroman-4-ol (3):** C<sub>9</sub>H<sub>10</sub>OS Uncolored oil. Yield = 90%. R<sub>f</sub> = 0.18. Eluent (v,v): petroleum ether /ethyl acetate (80/20).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ:** 2 (m, 1H) ; 2,3 (m, 2H) ; 2.8 (m, 1H) ; 3.3 (dt, *J* = 12.3, 3 Hz, 1H) 4,76 (dd, *J* = 4.8, 3 Hz, 1H); 7.05–7.3 (m, 4H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ:** 21.5, 30.0, 66.5, 124.3, 126.7, 128.4, 130.3, 133.2, 134.6.

**Chiral HPLC:** *Chiralpak* OD-H column, t<sub>S</sub> = 25.15 min, t<sub>R</sub> = 31.65 min. Eluent (v,v): n-hexane/iPrOH: 95/5; flow rate: 0.5mL/min.

**1,2,3,4-tetrahydronaphthalen-1-ol (4):** C<sub>10</sub>H<sub>12</sub>O, Crude oil. Yield = 89%. R<sub>f</sub> = 0.21. Eluent (v,v): petroleum ether /ethyl acetate (80/20).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ:** 1.2-1.9 (m, 4H); 2 (br, OH); 2,8 (m, 2H); 4,7 (m, 1H); 7,1-7,28 (m, 3H); 7.4-7.5 (m, 1H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ:** 18.8; 29.2; 32.2; 68.1; 126.1; 127.57; 128.7; 138.8; 137.14.

**Chiral HPLC:** *Chiralpak IA* column, t<sub>S</sub> = 18.12min, t<sub>R</sub> = 19.93min. Eluent (v,v): hexane/iPrOH: 95/5; flow rate: 0.5mL/min.

**1-furan-2-yl-ethanol (5):** C<sub>6</sub>H<sub>8</sub>O<sub>2</sub>, Crude oil. Yield = 87%. R<sub>f</sub> = 0.2. Eluent (v,v): petroleum ether /ethyl acetate (80/20).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ:** 1.55 (d, 3H, *J* = 6.5 Hz, 3H); 2.1 (br, 1H) ; 4.89 (q, 1H) ; 6.24 (d, *J* = 3.2 Hz, 1H); 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H); 7.39 (dd, *J* = 1.8, 0.7 Hz, 1H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ:** 21.25; 63.61; 105.13; 110.14; 141.9 ; 157.58.

**GC-2010 Plus:** *Chiralpak* Shimadzu ChiralDex G-BP, t<sub>S</sub> = 24.3 min, t<sub>R</sub> = 24.95 min.

**1-thiophen-2-yl-ethanol (6):** C<sub>6</sub>H<sub>8</sub>OS, Crude oil. Yield = 85%. R<sub>f</sub> = 0.25. Eluent (v,v): petroleum ether /ethyl acetate (80/20).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ:** 1.62 (dd, *J* = 6.4, 3.2 Hz, 3H); 1.97 (br, 1H); 5.1 (q, *J* = 6.4, 2.7 Hz, 1H); 6.98 (m, 2H); 7.26 (m, 1H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ:** 25.2; 66.2; 123.7; 124.4; 126.6; 149.8.

**Chiral HPLC:** *Chiralpak* Whelk column, t<sub>S</sub> = 6.38 min, t<sub>R</sub> = 7.78 min. Eluent (v,v): n-hexane/iPrOH: 75/25; flow rate: 0.7mL/min.

### 2.3.2. Synthesis of racemic acetate (1a-6a):

The racemic acetate were synthesized by classical chemical acetylation via the corresponding racemic-alcohol (1equiv), using 1.5 equiv. of anhydride acetic, 1.2 equiv. of Et<sub>3</sub>N, and a catalytic amount of 4-dimethylaminopyridine (0.2 equiv) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub>. The final products were obtained pure after standard work-up in excellent yields. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of these products were in good agreement with the literature.



**2,3-Dihydro-benzofuran-3-yl acetate (1a):**  $C_{10}H_{10}O_3$  Crude oil. Yield = 70%.  $R_f = 0.60$ .  
Eluent (v,v): petroleum ether /ethyl acetate (80/20).

**$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$ :** 2 (s, 3H); 4.5 (dd, 1H); 4.6 (dd, 1H); 6.25 (dd,  $J = 4.8$  Hz, 1H,);  
6.94 -7.48(m, 4H).  **$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$ :** 21, 74.22, 75.9; 110; 121; 124.4; 126.7;  
131.2; 161; 170.8.

**Chiral HPLC:** *Chiralpak IA* column,  $t_S = 12.18$ . min,  $t_R = 12.75$  min. Eluent (v,v): n-hexane/  
iPrOH: 95/5; flow rate: 0.5 mL/min.

**Chroman-4-yl acetate (2a):**  $C_{11}H_{12}O_3$  Yellow oil, Yield=90%.  $R_f = 0.80$ . Eluent (v,v):  
petroleum ether /ethyl acetate (80/20).

**$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$ :** 2 (s, 3H,  $OCOCH_3$ ), 2.2 (m, 2H,  $CH_2$ ), 4.3 (m, 2H,  $OCH_2$ ), 5.9  
(t,  $J = 2$  Hz, 1H), 6.9 (m, 2H), 7.3 (m, 2H).  **$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$ :** 21.4; 29.7; 63; 65.2;  
116.7; 120; 120.19; 129.9; 131.3; 155.5; 170.

**Chiral HPLC:** *Chiralpak IA* column,  $t_R = 12.07$ . min,  $t_S = 12.8$  min. Eluent (v,v): n-  
hexane/EtOH: 99/01; flow rate: 0.5 mL/min

**Thiochroman-4-yl acetate (3a):**  $C_{11}H_{12}O_2S$ , Yellow oil, Yield= 81%;  $R_f = 0.75$ . Eluent (v,v):  
petroleum ether /ethyl acetate (80/20).

**$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$**  2 (s, 3H), 2.14 (m, 1H), 2.4 (m, 1H), 2.9 (dd, 1H), 3.3 (dd, 1H),  
6.07 (t,  $J = 6.5$  Hz, 1H), 7-7.3 ( $H_{arom}$ ),  **$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$**  21.06 ; 21.74 ; 63.71 ;  
125.09 ; 125.3; 126.5; 143.02 ; 170.

**Chiral HPLC:** *Chiralpak OD-H* column,  $t_R = 13.02$  min,  $t_S = 13.83$  min. Eluent (v,v): n-  
hexane/iPrOH: 95/5; flow rate: 0.5mL/min

**1,2,3,4-tetrahydronaphthalen-1-yl acetate (4a):** Crude oil, Yield: 90%;  $R_f = 0.71$ . Eluent  
(v,v): petroleum ether /ethyl acetate (80/20).

**$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$ :** 1.80-1.83 ( $m_a$ , 1H cyclic); 1.93-2.08 ( $m_a$ , 3H cyclic) ; 2.3 (s, 3H,  
-2OC- $CH_3$ ) ; 2.68-2.90 ( $m_a$ , 2H cyclic) ; 5.98-6.01 (t,  $J = 4.09$  Hz; 1H) ; 7.10-7.29 ( $m_a$ , 4H).  **$^{13}C$   
NMR (75MHz,  $CDCl_3$ )  $\delta$ :** 16.8; 21.19; 6.16; 26.4; 28 ; 62.6; 123.35; 125.35; 127.18; 132;  
135.6; 169.5.

**Chiral HPLC:** *Chiralpak IA* column, min,  $t_R = 8.78$  min,  $t_S = 9.26$ . Eluent (v,v): hexane/iPrOH:  
95/05; flow rate: 0.5mL/min.

**1-(fur-2-yl) ethyl acetate (5a):**  $C_6H_{10}O_3$  Yellow oil, Yield: 72%;  $R_f = 0.63$ . Eluent (v,v):  
petroleum ether /ethyl acetate (80/20).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ: 1.59 (d, *J* = 36.3 Hz, 3H), 2.07 (s, 3H), 5.97 (q, *J* = 36.3 Hz, 1H), 6.34 (m, 2H), 7.4 (dd, *J* = 32.1, 34.2 Hz, 1H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)** δ: 17.04; 21.46; 64.49; 107.17; 110.42; 142.46; 153.02; 170.

**GC-2010 Plus:** *Chiralpak* Shimadzu Chiraldex G-BP. Gradient 60°C for 20 min; 10°C/min; 180°C for 20 min. *t<sub>R</sub>* = 23.45 min, *t<sub>S</sub>* = 24.03 min

**1-(thien-2-yl)ethyl acetate (6a)** : C<sub>8</sub>H<sub>10</sub>O<sub>2</sub>S Yellow oil. Yield: 80%; *R<sub>f</sub>* = 0.58. Eluent (v,v): petroleum ether /ethyl acetate (80/20).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ: 1.67 (d, *J* = 36.6 Hz, 3H), 2 (s, 3H), 6.1 (q, *J* = 36.6 Hz, 1H), 6.9 (dd, *J* = 33.3, 34.5 Hz, 1H), 7.05 (d, *J* = 33.3 Hz, 1H), 7.2 (d, *J* = 34.5 Hz, 1H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)** δ : 20.76; 21.91; 67.71; 124.99; 125.67; 126.78; 144.19; 170.

**Chiral HPLC:** *Chiralpak* IA column, *t<sub>R</sub>* = 8.38 min, *t<sub>S</sub>* = 8.80 min. Eluent (v,v): n-hexane/iPrOH: 95/5; flow rate: 0.5 mL/min.

#### 2.4. Enzymatic hydrolysis of racemic acetate (1a-6a):

In a typical procedure, 1 mmol of the racemic acetate (**1a-6a**) is dissolved in 3 mL of THF before the addition of 1 mmol of sodium carbonate and 40 mg of *CAL-B*. The mixture was stirred at 40°C for 72 h. After removal of the enzyme by filtration and evaporation of the solvent, the reaction mixture was purified by flash chromatography (Ep/EtOAc: 95/5) to separate the residual (*R*) or (*S*)-acetate and the furnished (*S*) or (*R*)-alcohol. The two enantiomers were analyzed by chiral HPLC.

#### 2.5. Deracemization through a selective alkaline-enzymatic hydrolysis/Mitsunobu esterification sequence:

Racemic acetates **1a-6a** (2 mmol), dissolved in 3 mL of tetrahydrofuran, were added to of immobilized lipase from *Candida antarctica B*. The reaction mixture was then stirred at 40 °C for the indicated time until the conversion reached *C* = 50%. The reaction was stopped by filtering off the solid enzyme on celite. The crude mixture of the (*S*)-acetate and unreacted (*R*)-alcohol in 4 mL THF. To this solution were added AcOH (0.144 g, 2.4 mmol) and PPh<sub>3</sub> (0.628 g, 2.4 mmol). The reaction mixture was immediately cooled to 0°C and a solution of diisopropylazodicarboxylate (DIAD) (0.48 g, 2.4 mmol) was added dropwise, under vigorous stirring during 20 min. The mixture was allowed to warm to room temperature and stirred for 24 h. Concentration of reaction mixture in *vacuo* followed by silica gel column chromatographic purification of the residue using hexane and ethyl acetate (8:2) gave only the (*S*)-acetates **1a-6a** in 70%–88% yield.

### 3. Results and discussion:

All racemic alcohols are obtained quantitatively *via* reduction of the corresponding ketones using sodium borohydride. All racemic acetates are obtained quantitatively *via* classical chemical acylation of the corresponding alcohols. All products are well characterized with spectroscopic analyses ( $^1\text{H}$  and  $^{13}\text{C}$  NMR).

#### 3.1. CAL-B-catalyzed alkaline-hydrolysis of (1a-6a) in non aqueous media:

The enzymatic hydrolysis reactions of acetates (**1a-6a**) were carried out on equimolecular mixture of racemic acetate and sodium carbonate in the presence of 40 mg of lipase CAL-B, in THF. The evolution of the reactions was checked by TLC. (scheme 2)

#### Scheme 2. Enzymatic-alkaline hydrolysis

After three days at 40°C, the lipase was filtered. The enantiomeric excesses of the (*S*)-remaining acetates and the (*R*)-recovered alcohols were evaluated by chiral HPLC or chiral GC. The obtained results are collected in **Table 1**.

The CAL-B catalyzed hydrolysis in basic medium ( $\text{Na}_2\text{CO}_3$ ) showed an excellent selectivity ( $E \gg 200$ ) in all cases. The (*R*)-alcohols (**1-6**) and the (*S*)-acetates (**1a-6a**) are obtained with high enantiomeric excesses ( $99\% \leq ee \leq 85\%$ ) at optimum conversions ( $46\% \leq \text{Conv} \leq 50\%$ ) (**Table 1**). The size of the cycle and the oxygen rapprochement to the stereogenic center (**1a-2a**) don't affect the reactivity and the selectivity of the CAL-B. Also, switching of oxygen (**2a**) by sulfur (**3a**) doesn't destabilize the CAL-B-catalytic site. This fact may attribute to absence of any disturbances due to stereoelectronic constraints exhibited by the nature of the heteroatom (entry 4 versus 2 & 3).

The resolution of the acetate (**4a**) is examined and allows to checking the impact of the electro-negativity of the heteroatom (sulfur and oxygen) on the stability of stereospecific pocket of the CAL-B. The heteroatom incorporated into the aromatic ring (**5a-6a**) has no significant influence on the performance of the CAL-B under the kosmotropic effect of the monovalent cation ( $\text{Na}^+$ ) in the organic medium. No influence is recorded and all the substrates resolved fit well with the active site of this serine-hydrolase.

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2  
3 **Table1:** *CAL-B*-catalyzed Kinetic resolution via hydrolysis of acetates (**1a-6a**) in the presence  
4 of Na<sub>2</sub>CO<sub>3</sub>:  
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8 It is interesting to note that the acylation of alcohols (**2-6**) by vinyl acetate was also selective,  
9 in a previous work; the acetates (*R*)-(**2a-6a**) were obtained with high selectivities *via CAL-B*-  
10 catalyzed transesterification (Melais et al. 2015). Thus the hydrolysis and acylation reactions  
11 catalyzed by *CAL-B* are enantiocomplementary.  
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15 In this work, the enantiomers of 2,3-dihydrodrobenzo-2-ol were obtained with high  
16 enantiomeric excesses between 97-99%, through an enzymatic kinetic resolution (entry 1)  
17 *via* an alkaline hydrolysis (figure 1).  
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23 **Figure 2:** HPLC chiral analyses of results of alkaline enzymatic resolution of *rac-1a*  
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### 28 **3.2. Deracemization through a selective alkaline-*CAL-B* hydrolysis/ Mitsunobu** 29 **esterification sequence.** 30

31 Following of the high reactivities and selectivities in the kinetic resolution catalyzed with the  
32 *CAL-B* lipase in the presence of Na<sub>2</sub>CO<sub>3</sub>, we have combined enzymatic alkaline hydrolysis to  
33 the Mitsunobu esterification protocol to leads deracemization *via* stereoinversion, the two  
34 steps were carried out in one pot. For that, the acetates (**1a-6a**) were hydrolyzed according  
35 the conditions established below.  
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41 After three days at 40°C, the *CAL-B* was filtered. The enantiomeric excesses of the  
42 remaining acetate and the recovered alcohol were evaluated by chiral HPLC or chiral GC.  
43 Directly, to the filtrate, 1.2 equivalent of triphenyl phosphine, and 1.2 equivalent of acetic acid  
44 were added. The diisopropylazodicarboxylate (DIAD) (1.2 equivalent) was added slowly at  
45 0°C, to convert the (*R*)-alcohols into the (*S*)-acetates. The desired acetates was then isolated  
46 after standard work up and purification by silica-gel column chromatography. The  
47 enantiomeric purity was determined by chiral HPLC or chiral GC, and the absolute  
48 configurations were determined by the sign of optical rotation and comparison to the  
49 literature data. (**scheme 3**)  
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56 **Scheme 3:** Deracemization through a selective alkaline enzymatic hydrolysis / Mitsunobu  
57 esterification sequence.  
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3 The results detailed in scheme 3, show that the (*S*)-acetates (**1a-6a**) were obtained  
4 quantitatively (70% ≤ yield ≤ 84%). It was found that the enantiomeric purity of the acetates  
5 recovered is dependent to the acetate structure. With the heterocyclic carbinols (**1-3**), in the  
6 Mitsunobu esterification, the deracemization was done smoothly, with little bit lose of the  
7 enantiopurities of the formed acetates (5% ≤ Δee ≤ 10%). Despite the high ee of both  
8 enantiomers recovered from the enzymatic resolution (ee ≥ 98%), the (*S*)-acetates (**1a-3a**)  
9 are obtained with (88% ≤ ee<sub>(S)</sub> ≤ 92%). On the other hand, with the heteroaromatic carbinols  
10 (**5-6**), a notable drop of enantiomeric purity of the recovered acetates after the enzymatic  
11 resolution step (37% ≤ Δee ≤ 49%). Where the (*S*)-acetates (**5a-6a**) are obtained with (51% ≤  
12 ee<sub>(S)</sub> ≤ 62%). The loss of the enantiopurity of alcohols during the nucleophilic substitution  
13 (S<sub>N</sub>2) (Mitsunobu esterification) was attributed to partial stereoinversion. Or else, this  
14 phenomenon of drop of optical purity may arise in the case of benzylic alcohol, from a  
15 competitive substitution process proceeding *via* an attack of the carbocation intermediate  
16 formed by nucleophile *via* a non-stereoselective (S<sub>N</sub>1) process to generate the racemic  
17 product (Warmerdam et al. 1993; Hillier et al. 2004; Houiene et al. 2013), which in our case  
18 will give rise to an overall decrease of the enantiomeric excess of recovered (*S*)-acetates.  
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30 Finally, except chromanols derivatives (Ashley et al. 2017), the deracemization of acetates  
31 (**1a**, **5a** and **6a**) subject of the present work are not previously investigated through other  
32 deracemization methodologies. Furthermore the deracemisation of (**1a-6a**) *via* alkaline  
33 enzymatic hydrolysis / stereoinversion process is not described yet.  
34  
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#### 40 **4. Conclusion**

41 In the present work, we have applied the *CAL-B*-catalyzed kinetic resolution by hydrolysis in  
42 the presence of Na<sub>2</sub>CO<sub>3</sub> and we have got both enantiomers of some heterocyclic and  
43 heteroaromatic carbinols enantiomerically pures.  
44  
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46

47 The enzymatic hydrolysis of the acetates **1a**, **2a** and **3a** was not described yet. We have  
48 obtained those acetates enantiomerically pures from the highly selective alkaline-enzymatic  
49 hydrolysis (Conv = 50% and E > 200). Furthermore, the successful enzymatic kinetic  
50 resolution of 2,3-dihydrobenzofuran-3-ol and of their acetate was given for the first time.  
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55 To valorise the obtained results of the kinetic resolution by improving the atom efficiency, we  
56 have combined to the Mitsunobu stereoinversion protocol to recycling one of the formed  
57 enantiomers, in our case, the (*R*)-alcohol. The recovered (*S*)-acetates after the  
58 stereoinversion protocol were isolated quantitatively, allowing overcoming the maximum of  
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3 50% yield which could be usually reached in a regular kinetic resolution. The (S)-acetates  
4 (1a-3a) are obtained with good enantiomeric excesses ( $88\% \leq ee \leq 92\%$ ). Otherwise, for the  
5 heteroaromatic structures (5a-6a) the Mitsunobu esterification stereoinversion step was  
6 suffered of an important drop of enantiomeric excesses.  
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### 10 **Acknowledgments**

11 Algerian Ministry of Higher Education and Scientific Research (MESRS, FNR 2000) is  
12 gratefully acknowledged for the financial support of this work. Emilie Kolodziej (Catalyse  
13 Moléculaire-ICMMO Paris-Sud University Orsay, France) is acknowledged for his assistance  
14 of Nabila Braia to perform some specific analyses.  
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### 19 **Disclosure statement**

20 No potential conflict of interest was reported by the author(s).  
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### 33 **Supporting information**

34 Additional supporting information may be found in the online version of this article at the  
35 publisher's web-site.  
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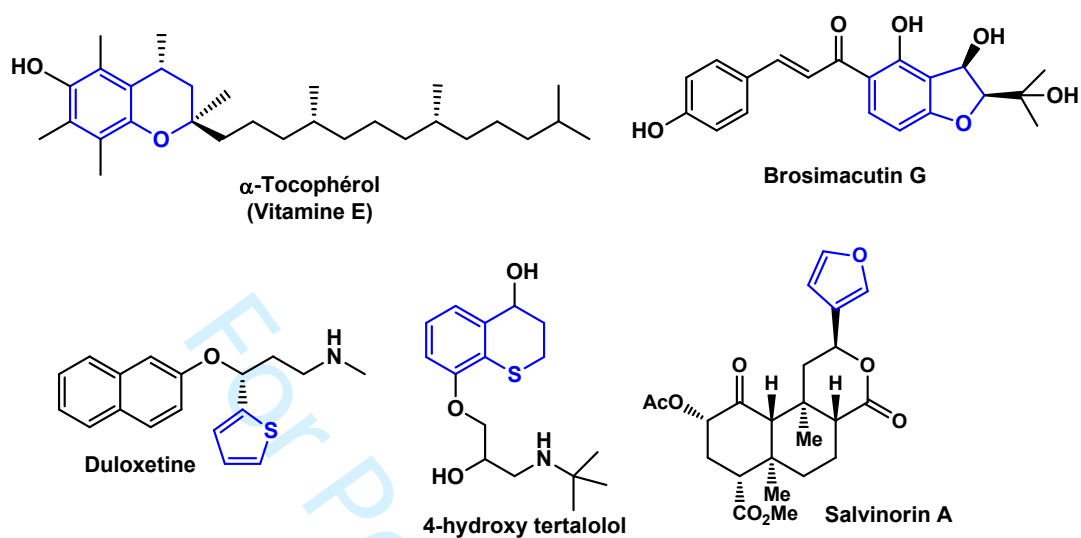
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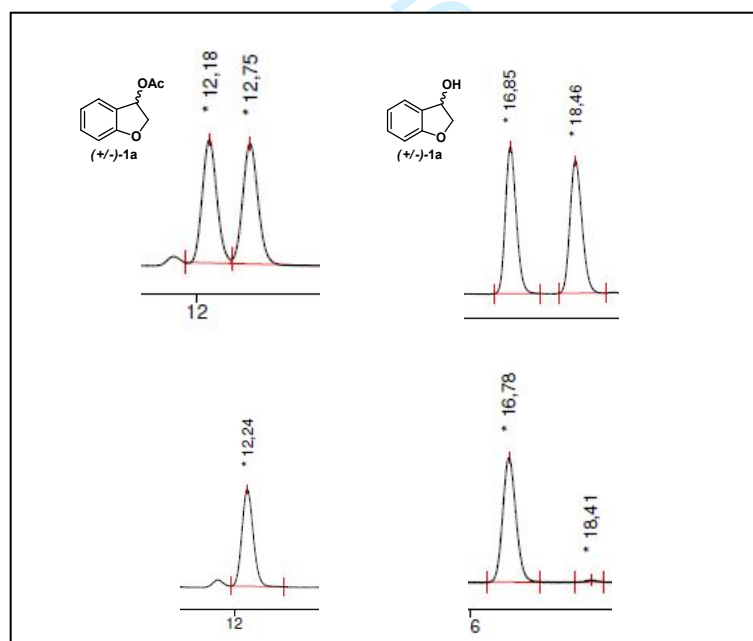
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## Figures

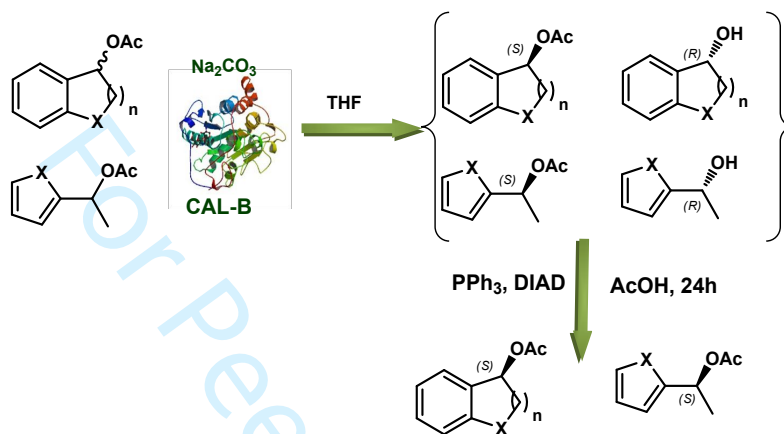
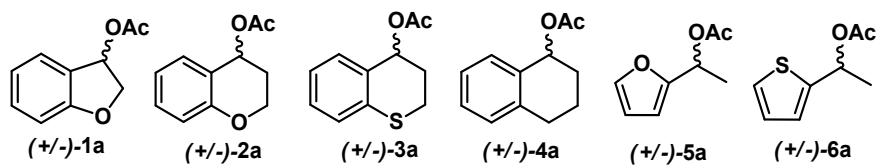


**Figure 1:** Some bioactive molecules within heterocyclic (aromatic) fragment.

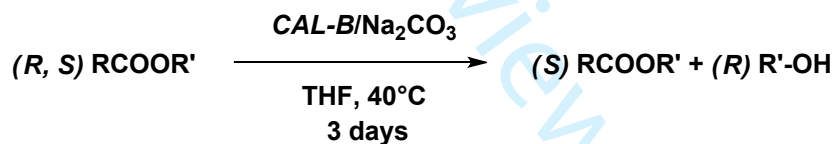


**Figure 2 :** HPLC chiral analyses of results of alkaline enzymatic resolution of *rac-1a*

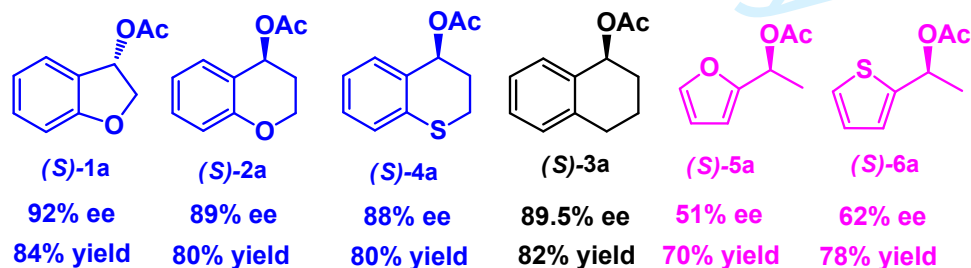
## Schemes



Scheme 1: Our present investigation



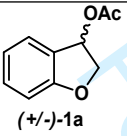
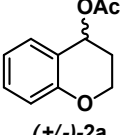
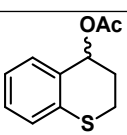
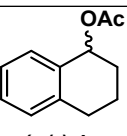
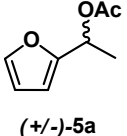
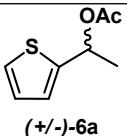
Scheme 2. Enzymatic-alkaline hydrolysis



Scheme 3: Deracemization through a selective alkaline enzymatic hydrolysis / Mitsunobu esterification sequence.

## Table

**Table1:** CAL-B-catalyzed Kinetic resolution via hydrolysis of acetates (**1a-6a**) in the presence of Na<sub>2</sub>CO<sub>3</sub>:

Entry <sup>a</sup>	Acetates	(S)-Acetate		(R)-Alcohol		Conv <sup>c</sup> (%)	E <sup>c</sup>
		ee <sub>S</sub> <sup>b</sup> (%)	Yield <sup>d</sup> (%)	eep <sup>b</sup> (%)	Yield <sup>d</sup> (%)		
1	 (+/-)-1a	>99	40	97	45	50	>200
2	 (+/-)-2a	>99	42	>99	46	50	>200
3	 (+/-)-3a	98	47	>99	47	50	>200
4	 (+/-)-4a	85	45	>99	40	46	>200
5	 (+/-)-5a	97	45	96	43	50	>200
6	 (+/-)-6a	>99	46	>99	45	50	>200

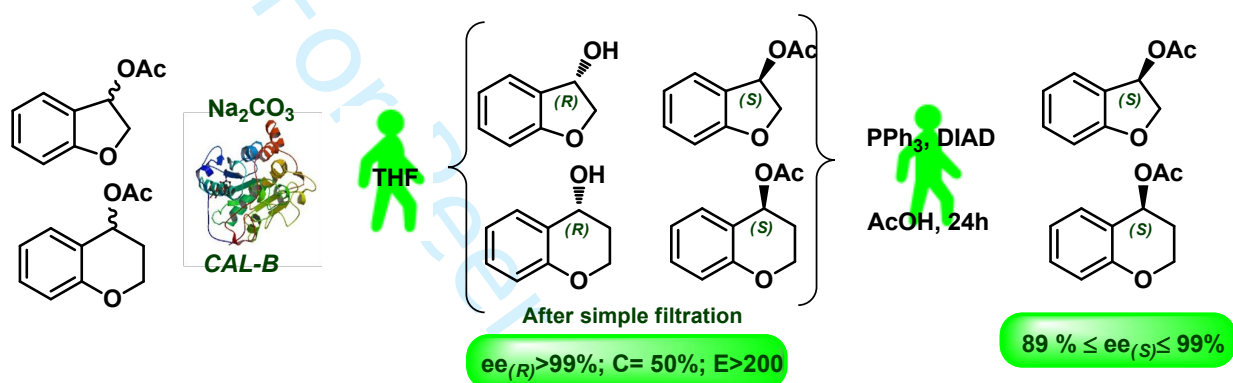
(a) 1mmol of racemic acetate, 1 mmol of Na<sub>2</sub>CO<sub>3</sub>, 40mg of CAL-B, 3 ml of THF at 40°C during 72 hours

(b) Enantiomeric excess of recovered products are measured by chiral HPLC or chiral GC.

(c) Conversion (Chen et al. 1982; Kagan and Fiaud 1988):  $Conv = ee_S / (ee_P + ee_S)$ ; Selectivity:  $E = \ln [(1-C) (1-ee_S)] / \ln [(1-C) (1+ee_S)]$

(d) Isolated yields.

## Graphical Abstract:



## Supporting information for:

### Practical access to (S)-heterocyclic aromatic acetates via CAL-B/Na<sub>2</sub>CO<sub>3</sub>-deacylation and Mitsunobu reaction Protocol.

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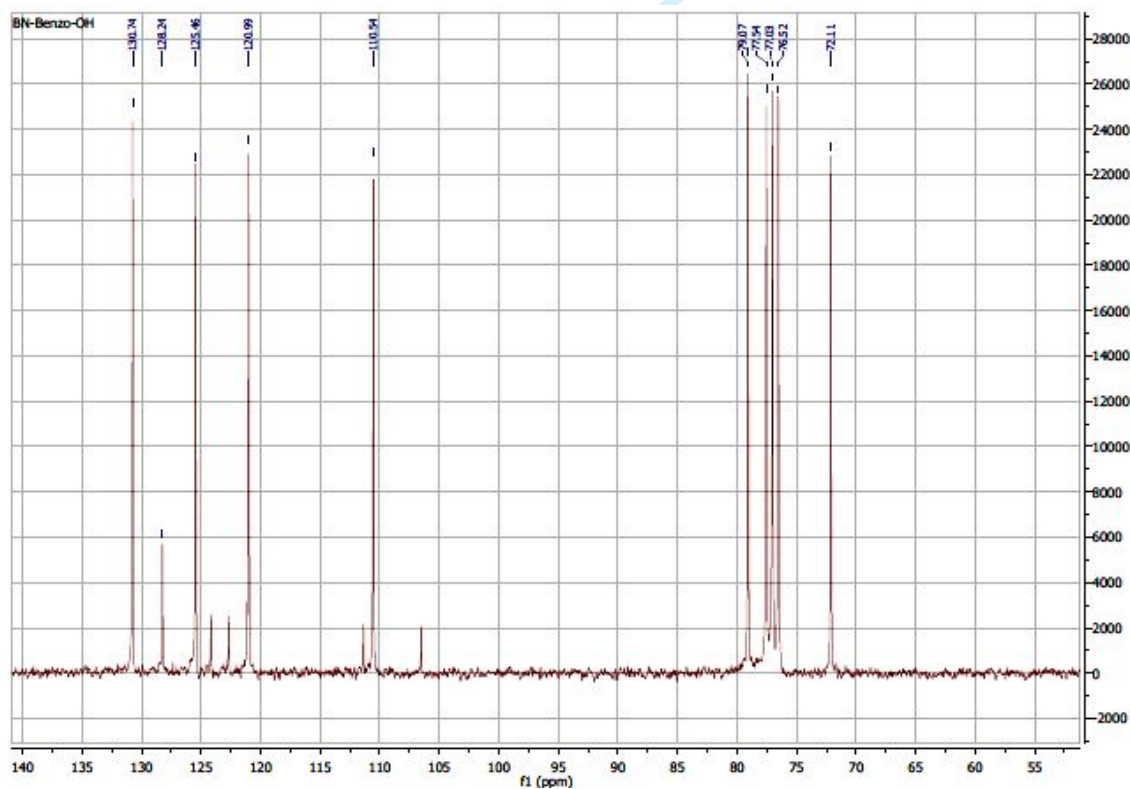
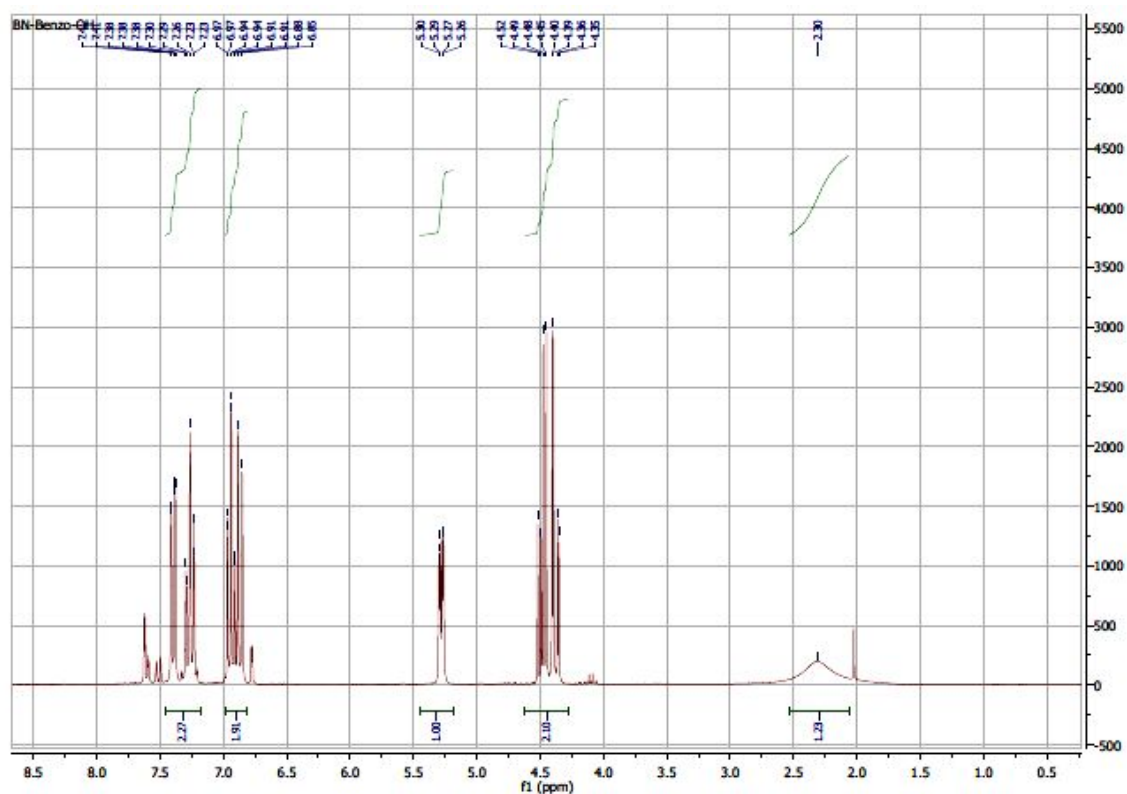
<sup>b</sup> Equipe de Catalyse Moléculaire-ICMMO Bât 420. Université Paris- Saclay

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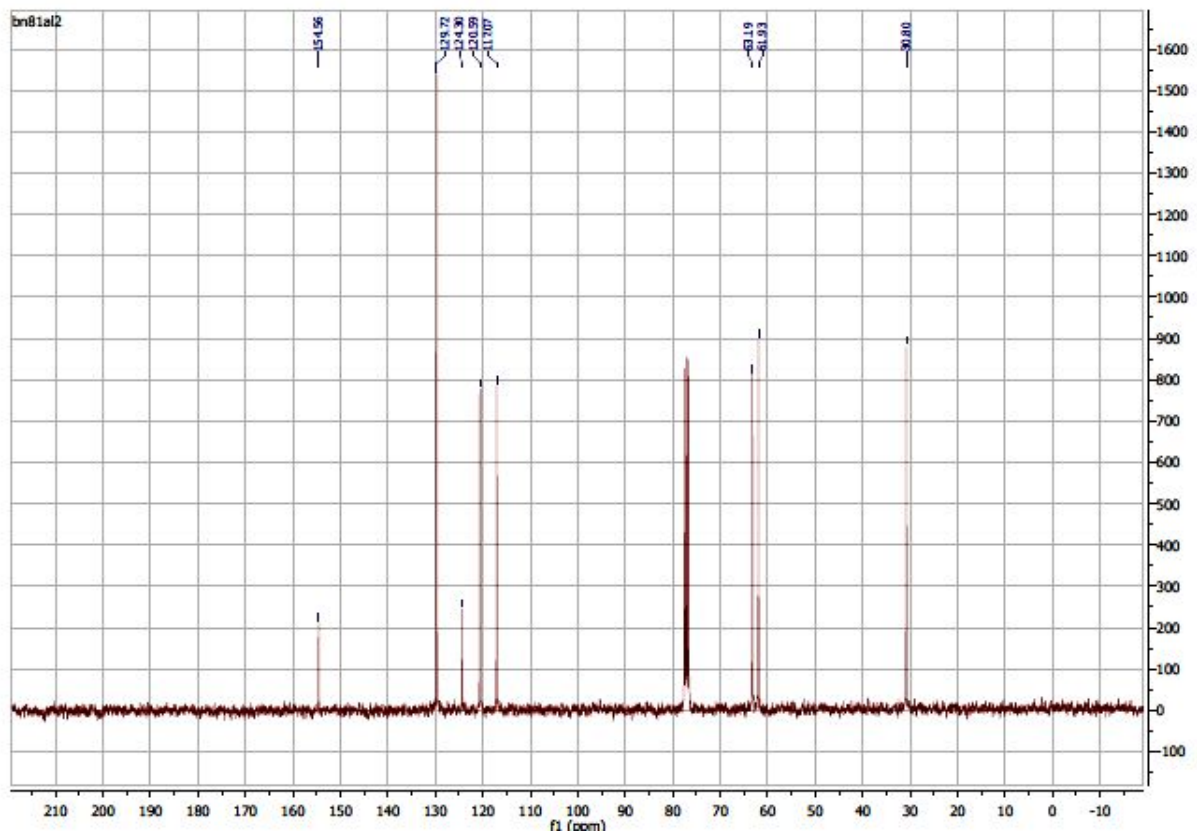
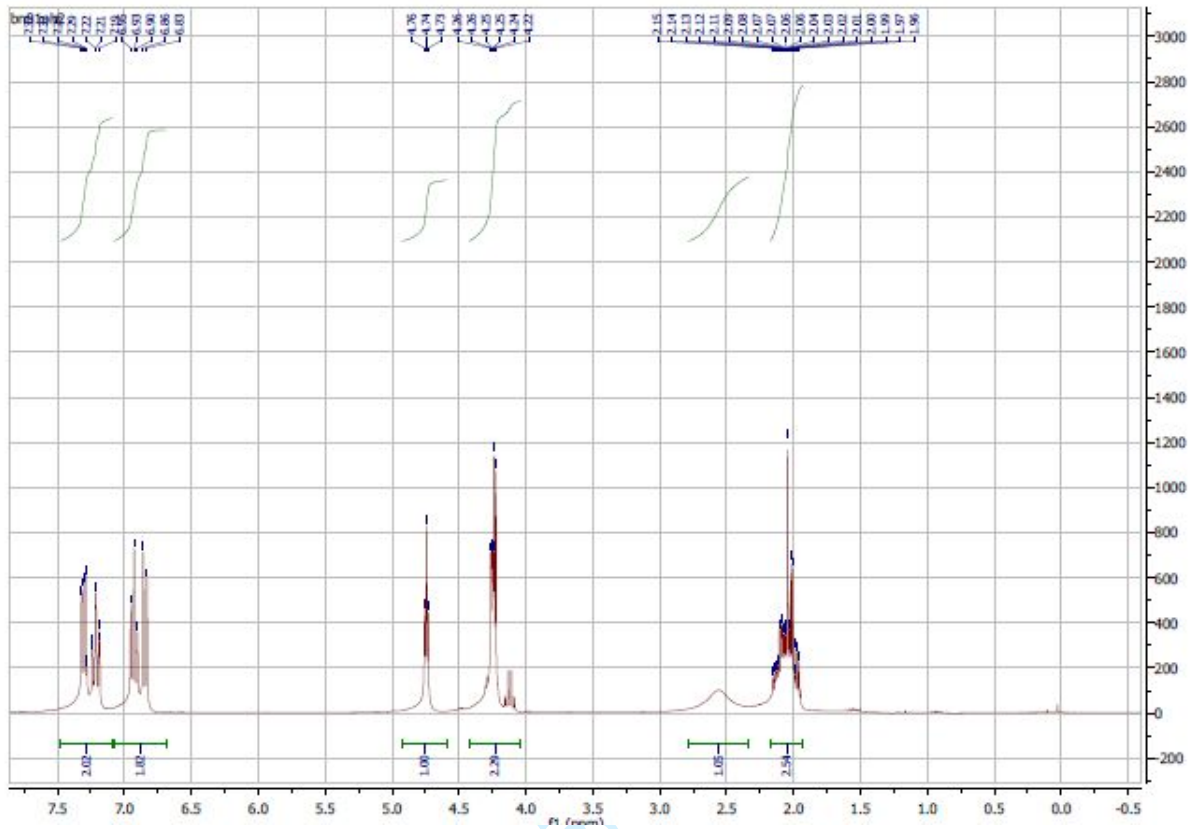
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# 1. NMR spectra of all racemic compounds

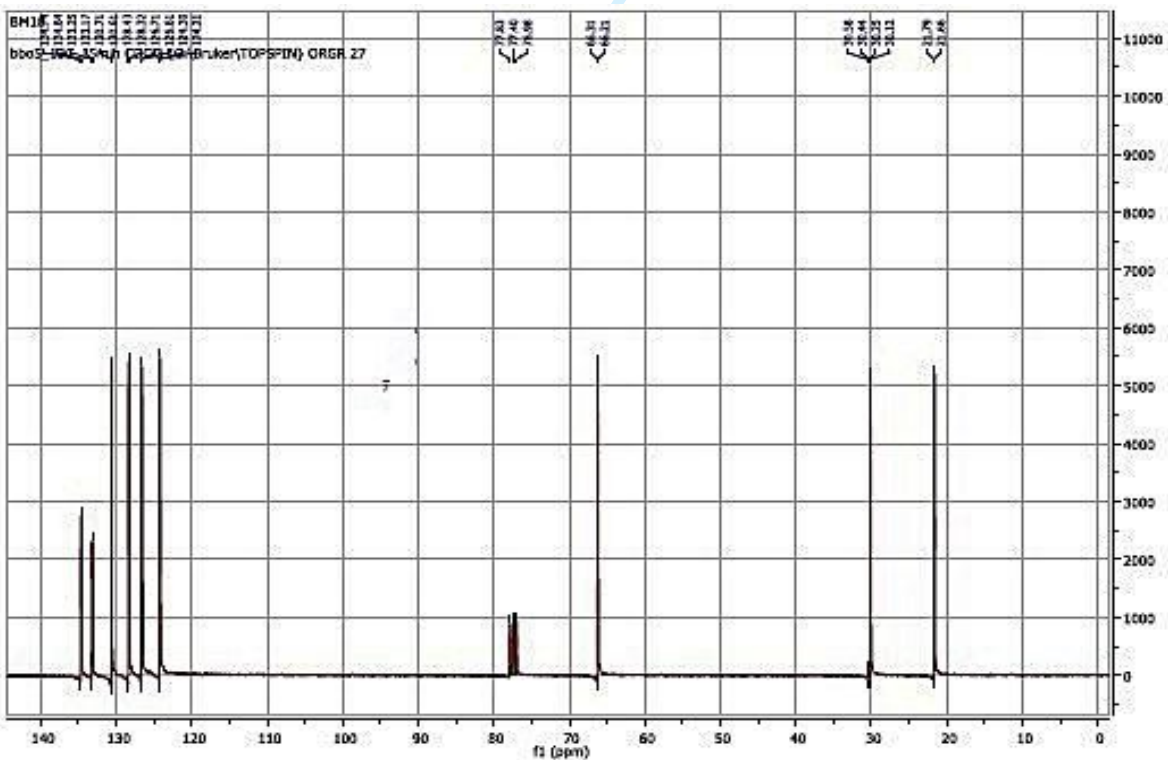
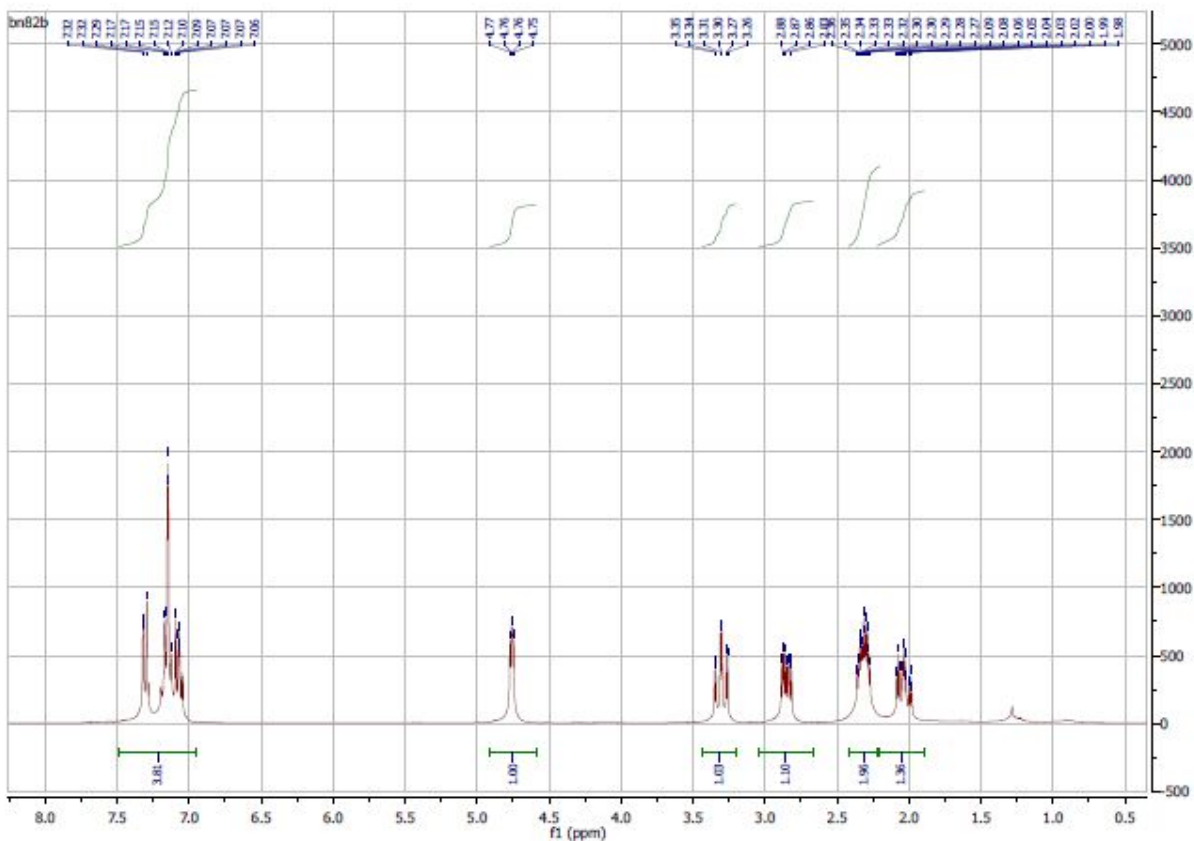
## 2,3-Dihydro-benzofuran-3-ol (1)

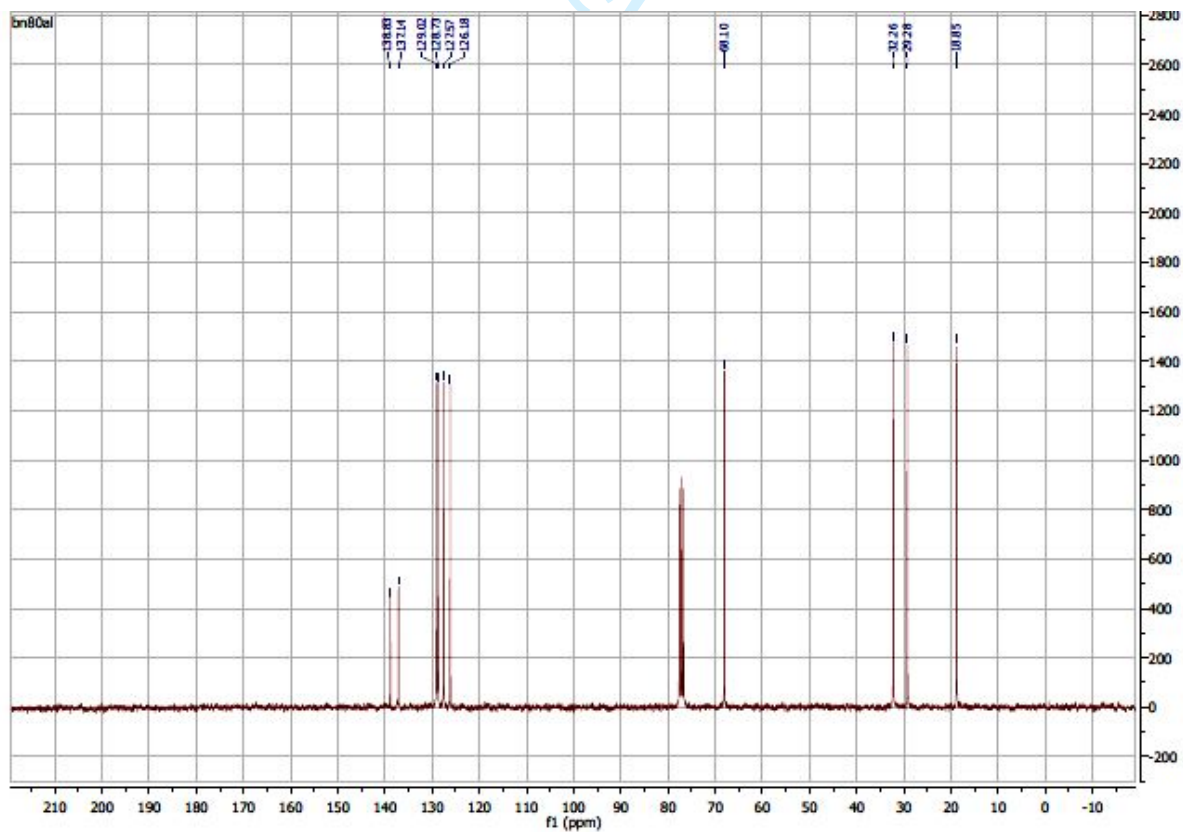
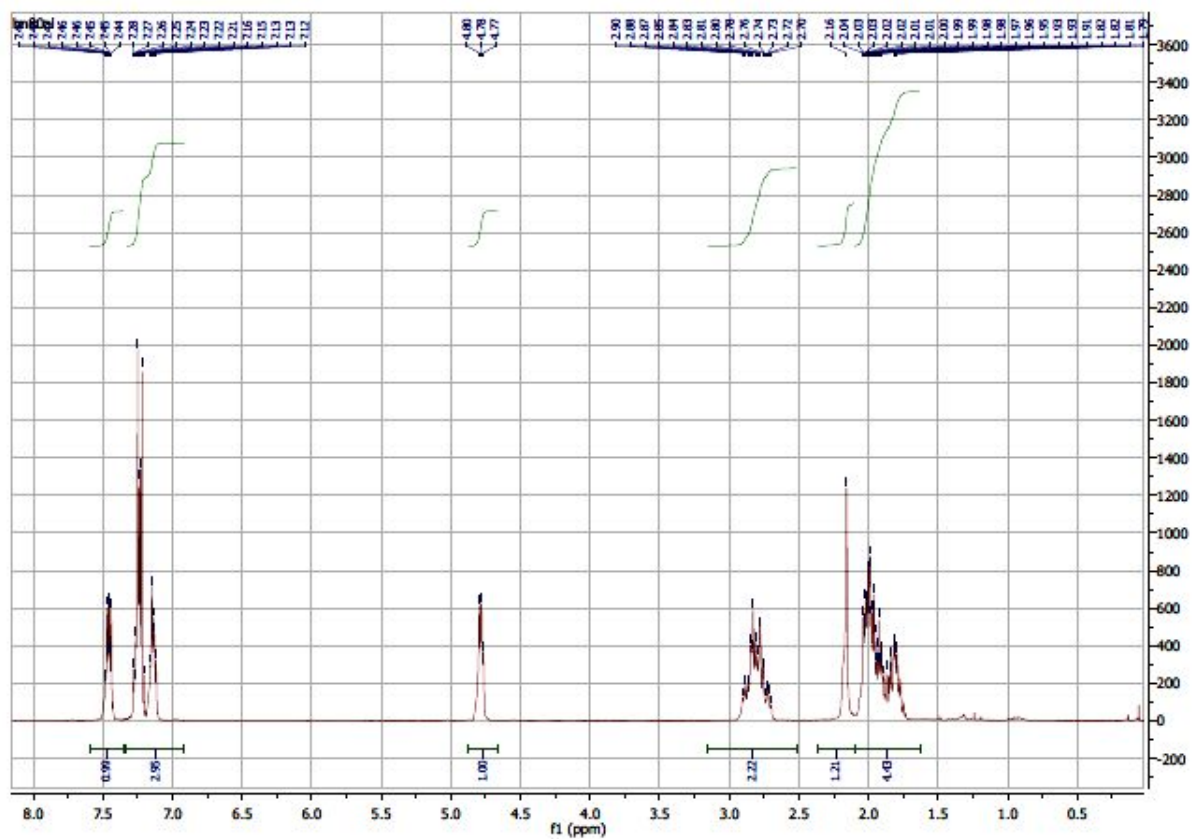


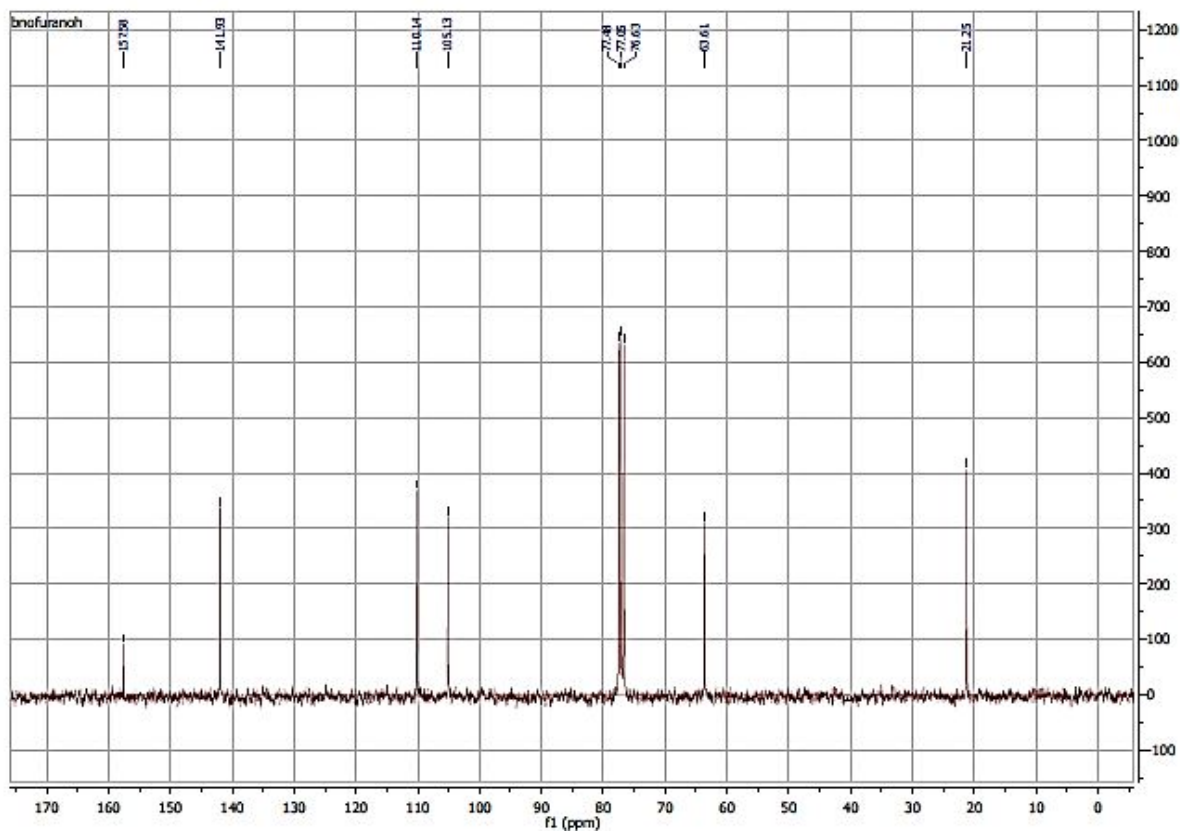
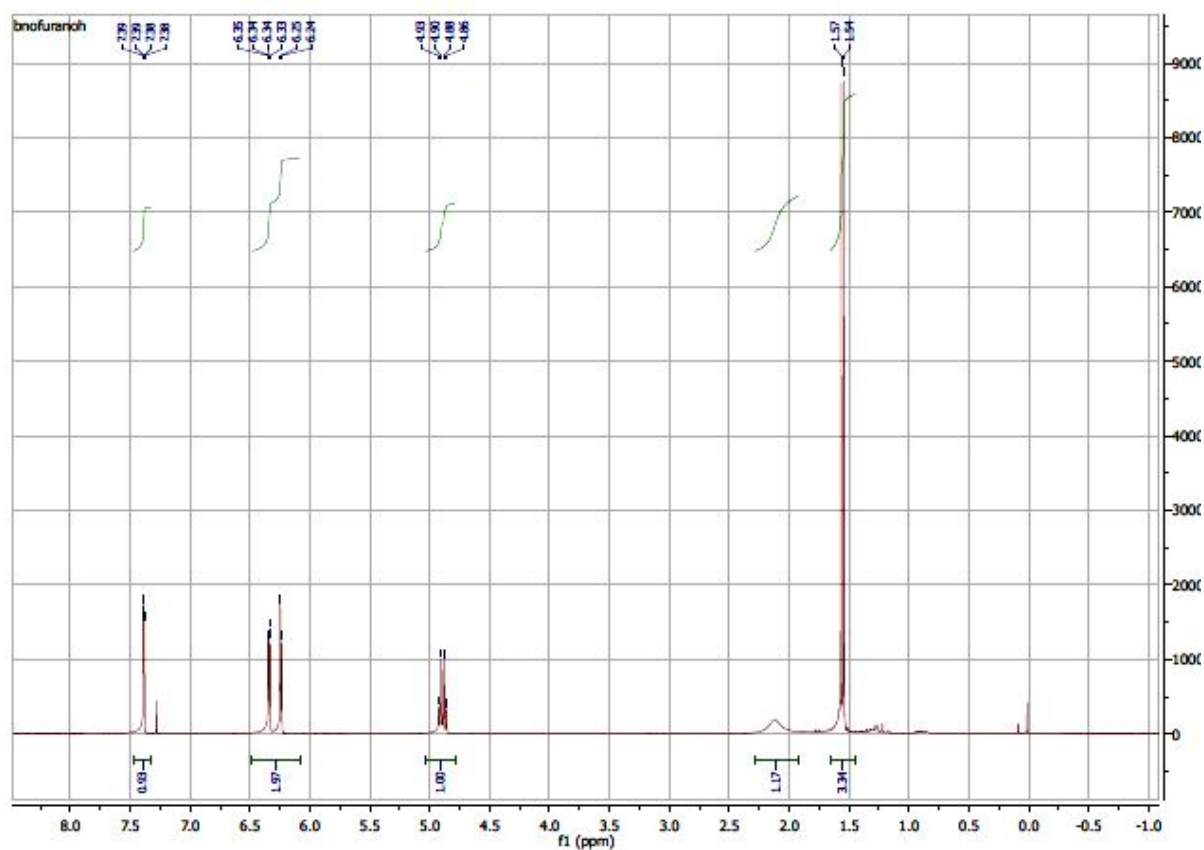


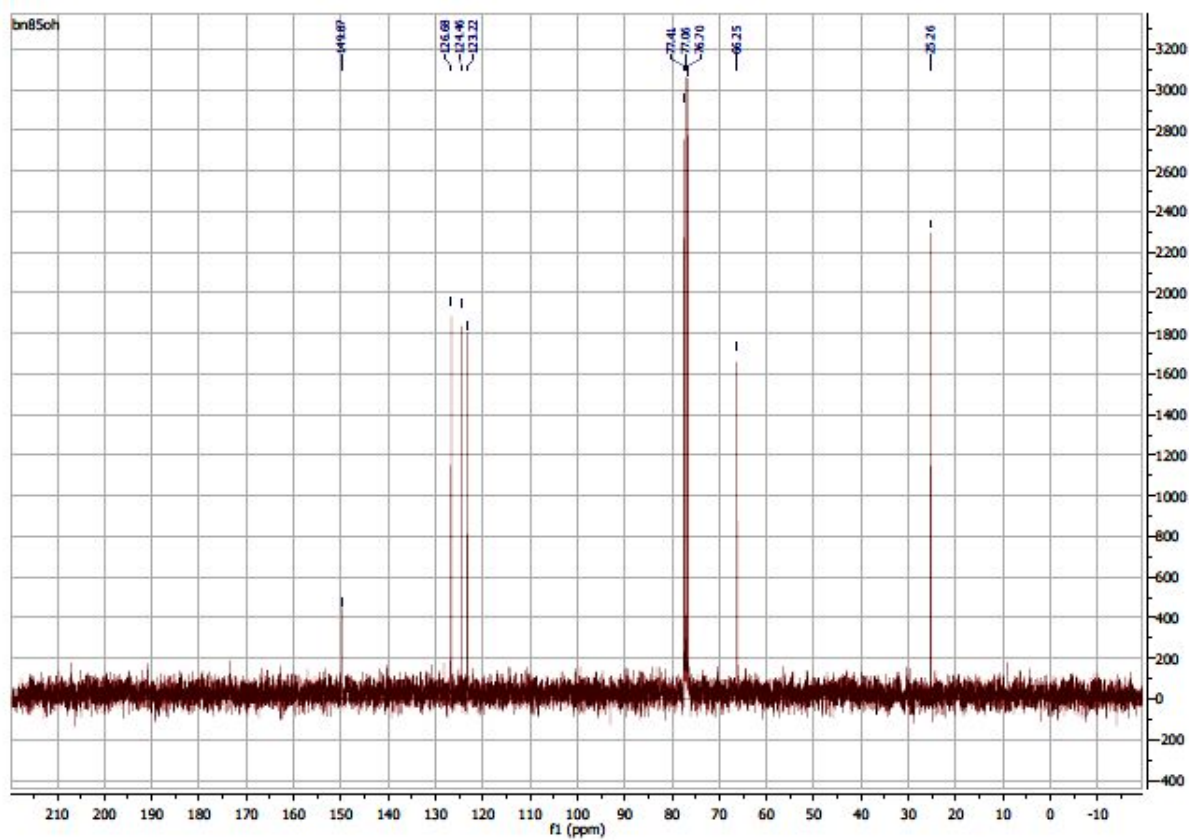
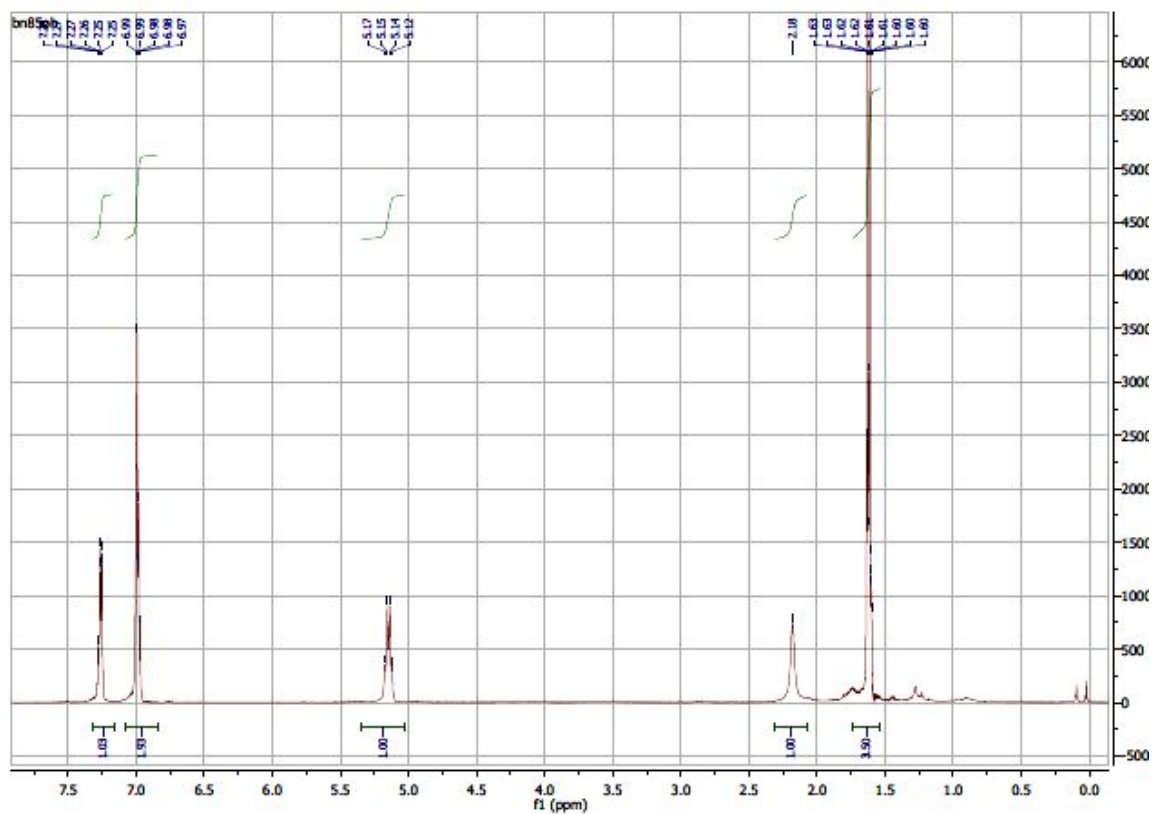
**Chroman-4-ol (2)**

2, 3-dihydrothiochroman-4-ol (3)

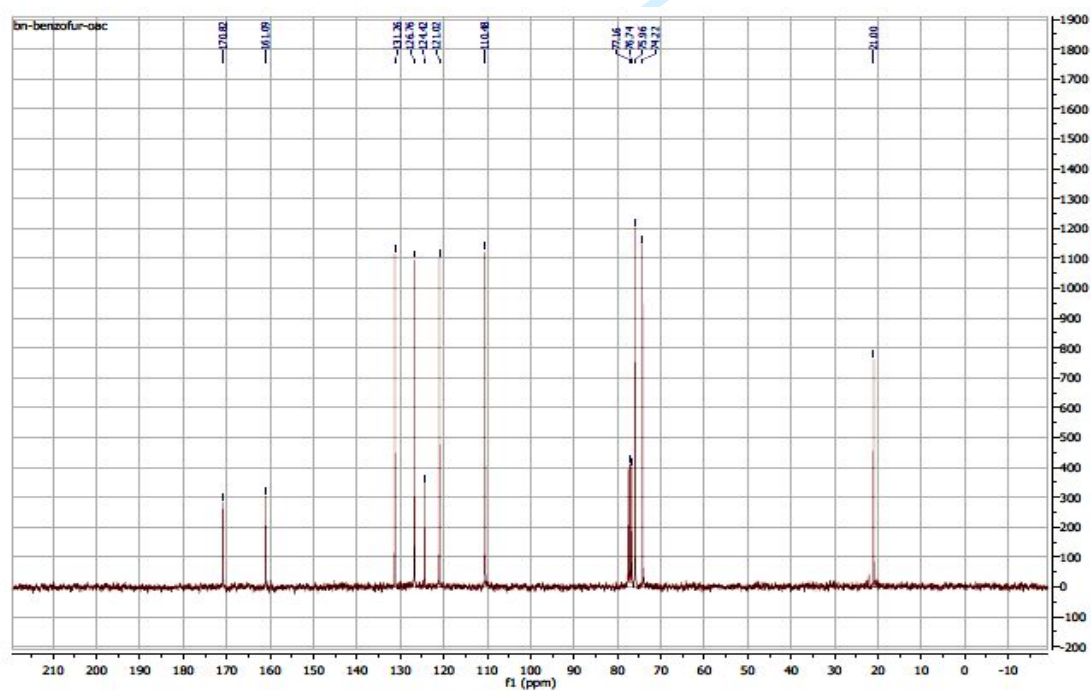
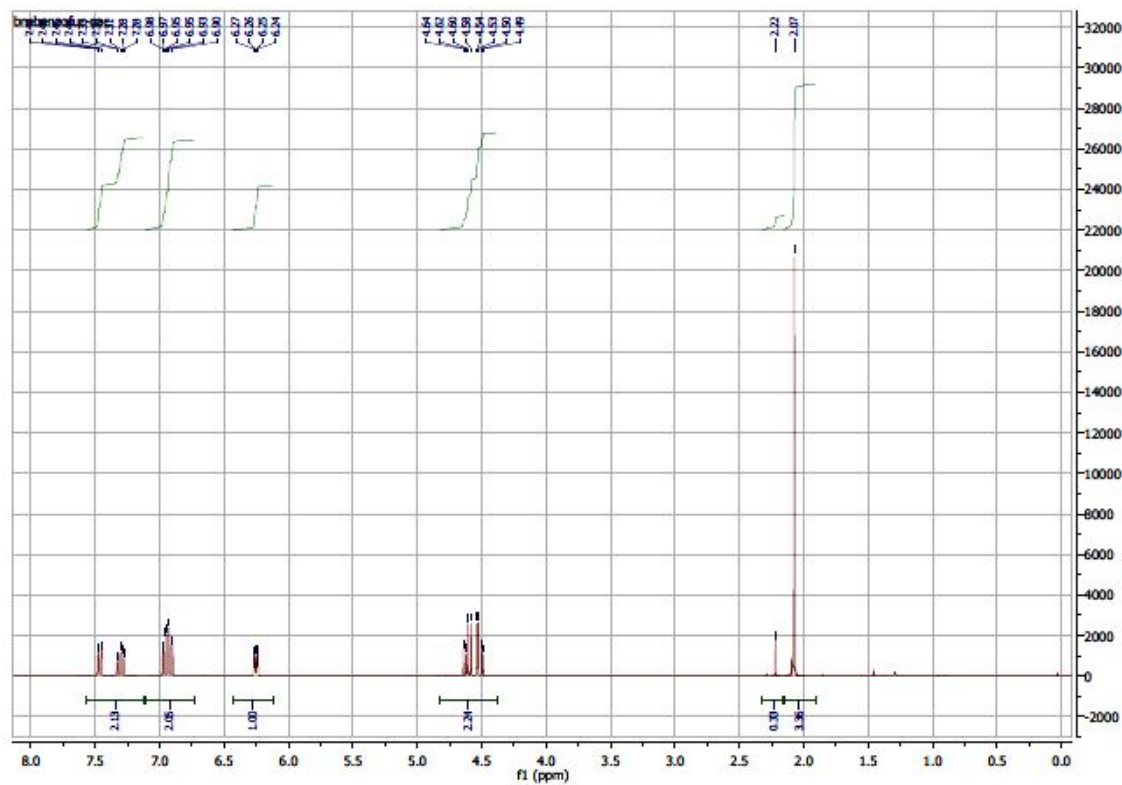


*1, 2, 3, 4-tetrahydronaphthalen-1-ol (4)*

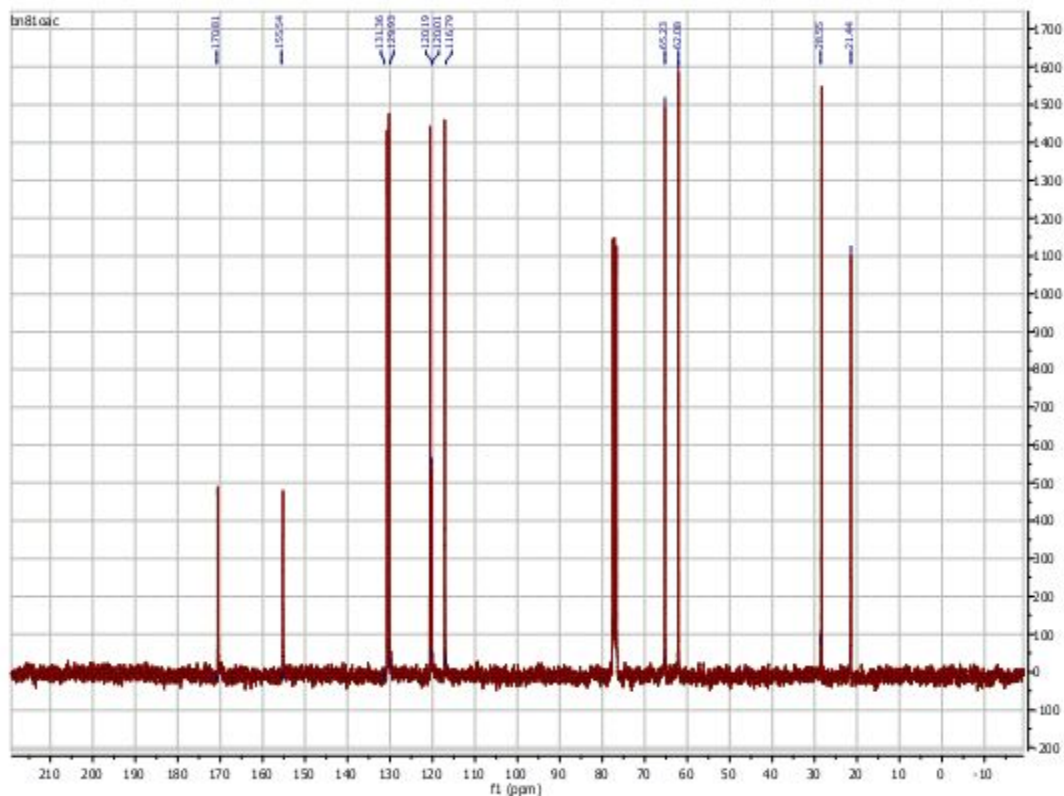
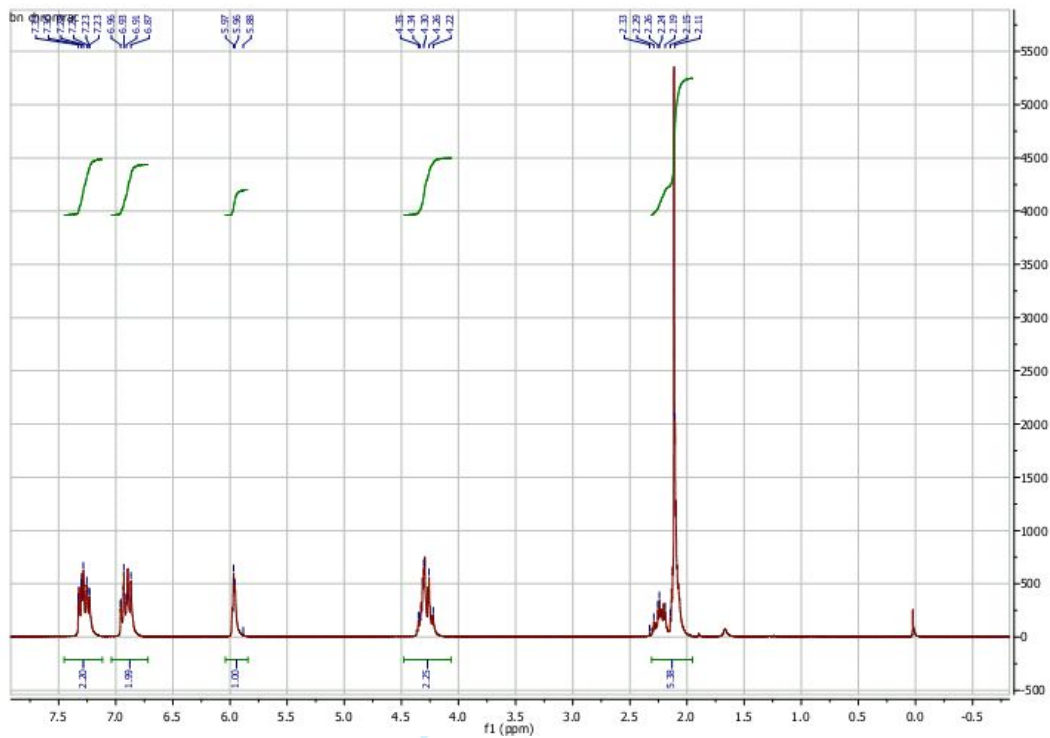
*1-furan-2-yl-ethanol (5)*

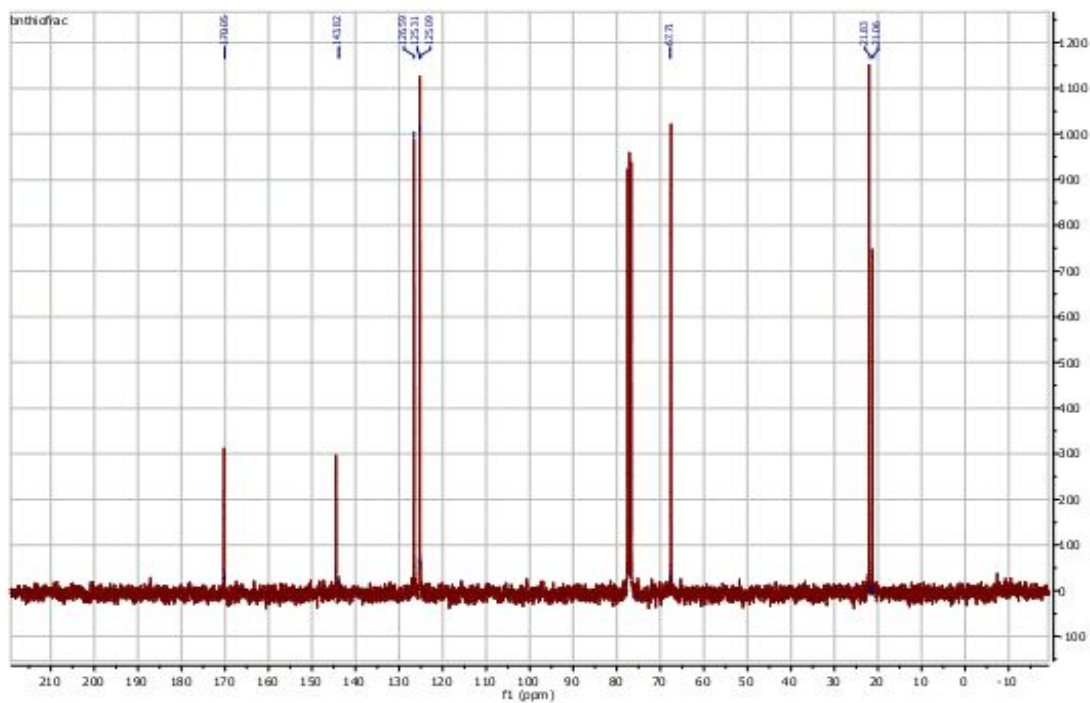
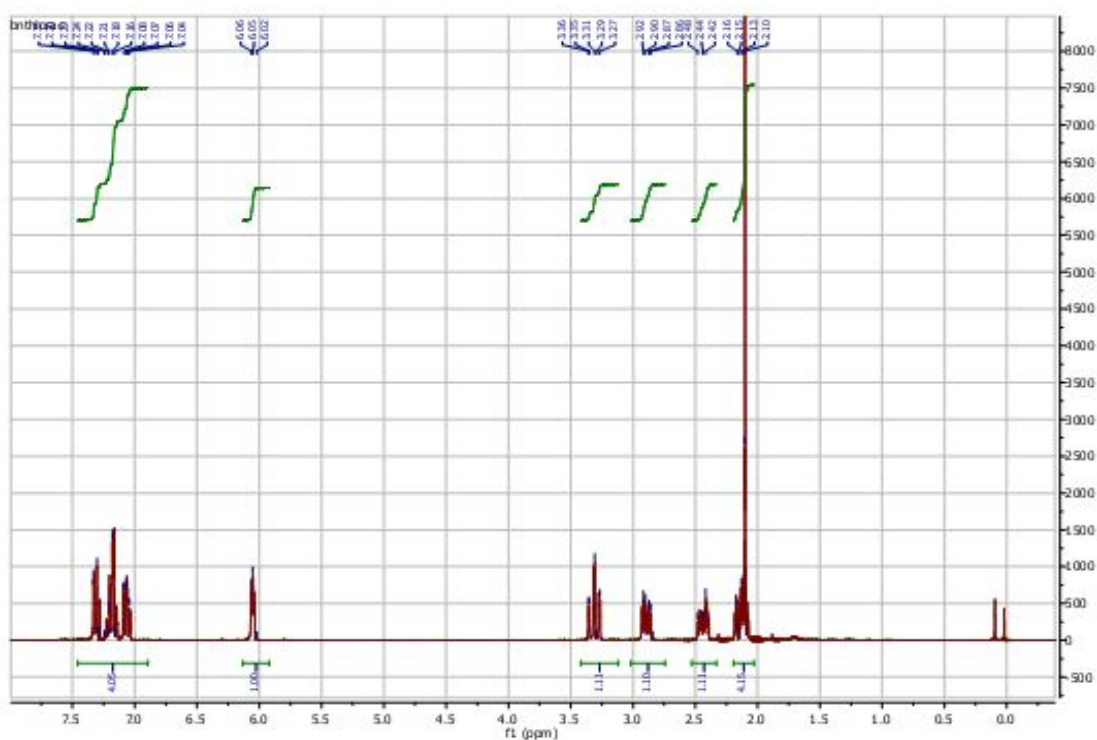
*1-thiophen-2-yl-ethanol (6)*

1  
2  
3 **2, 3-Dihydro-benzofuran-3-yl acetate (1a):**  
4  
5

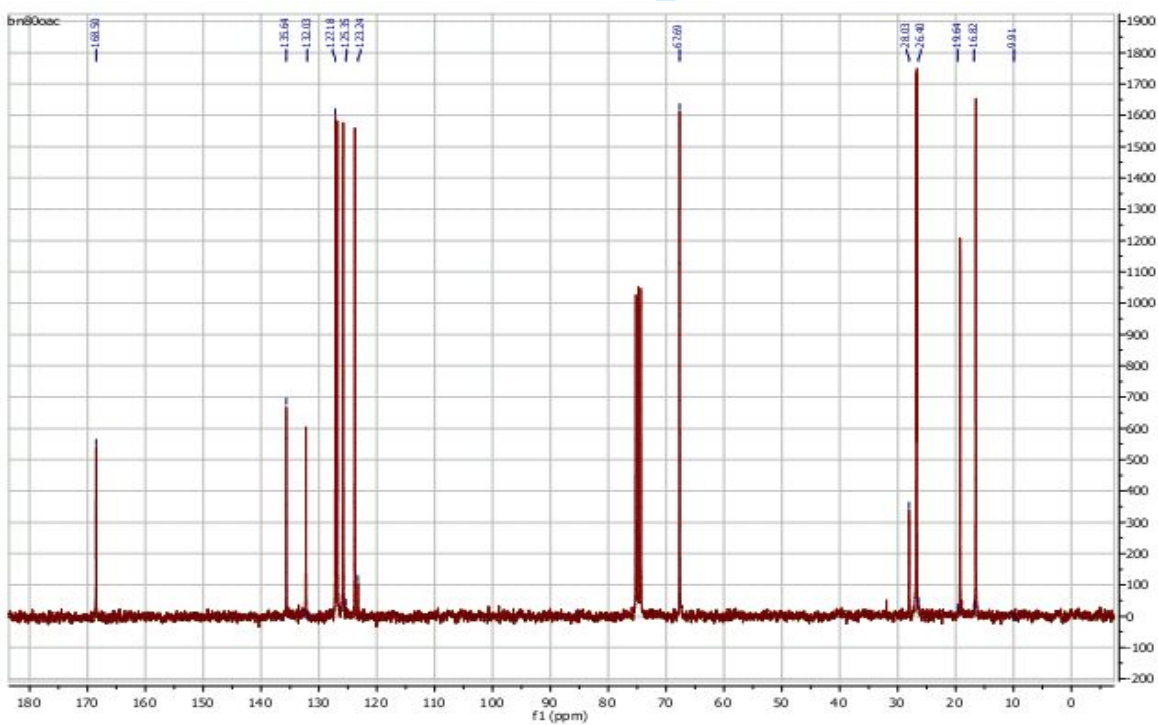
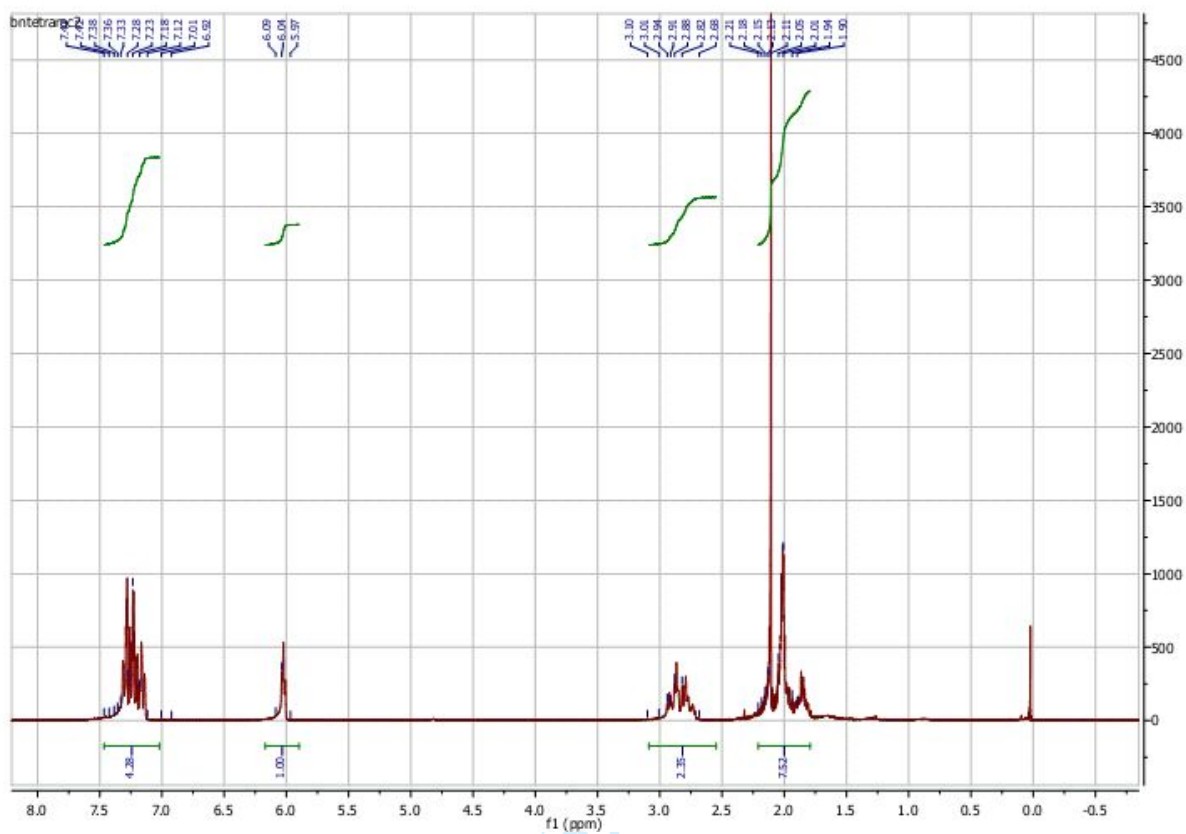


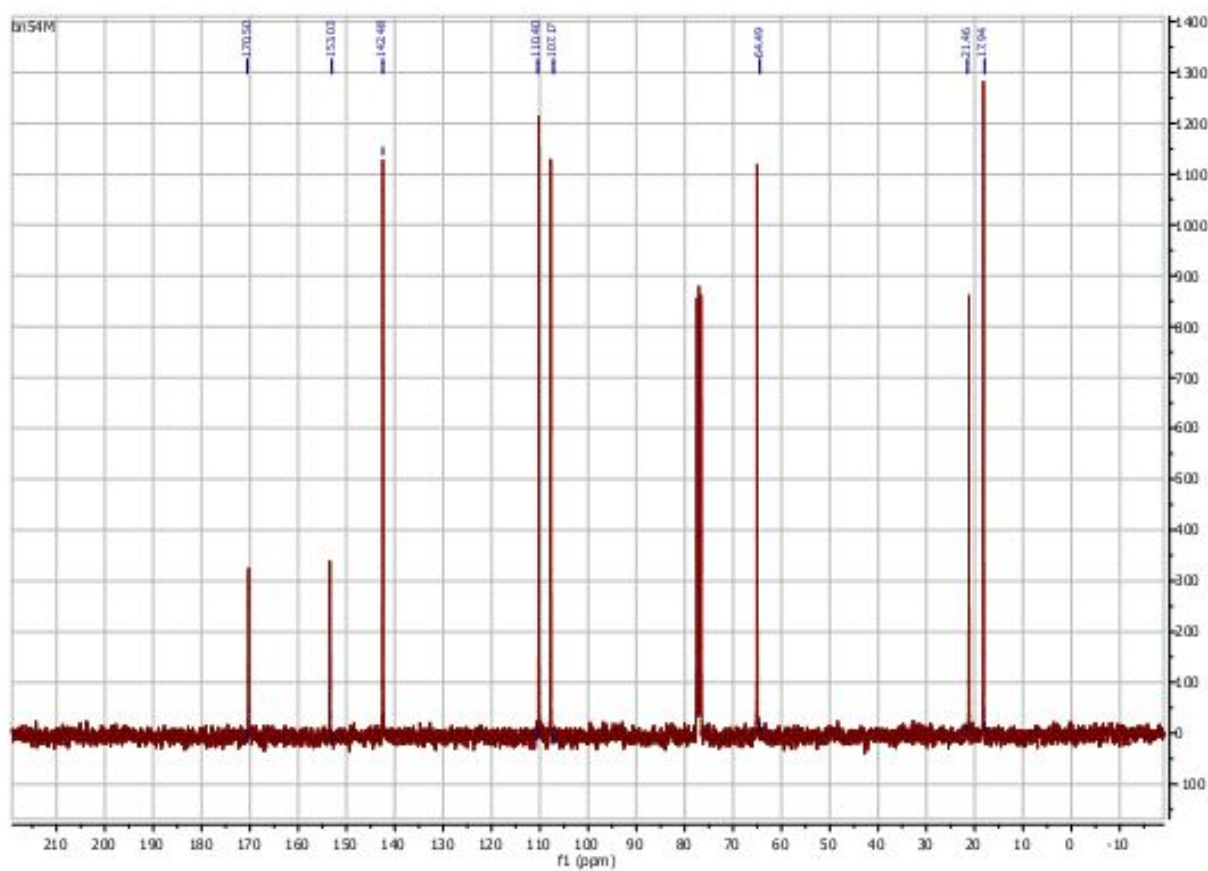
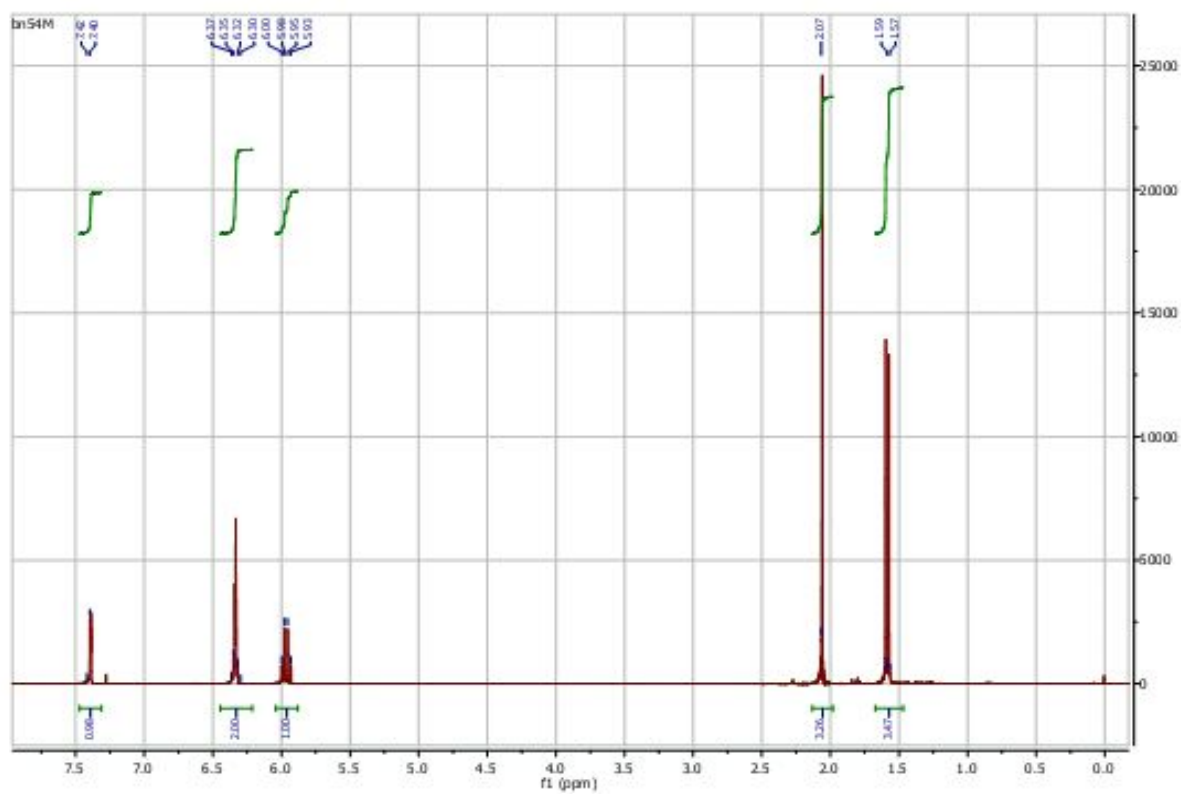
1  
2  
3 **Chroman-4-yl acetate (2a):**  
4

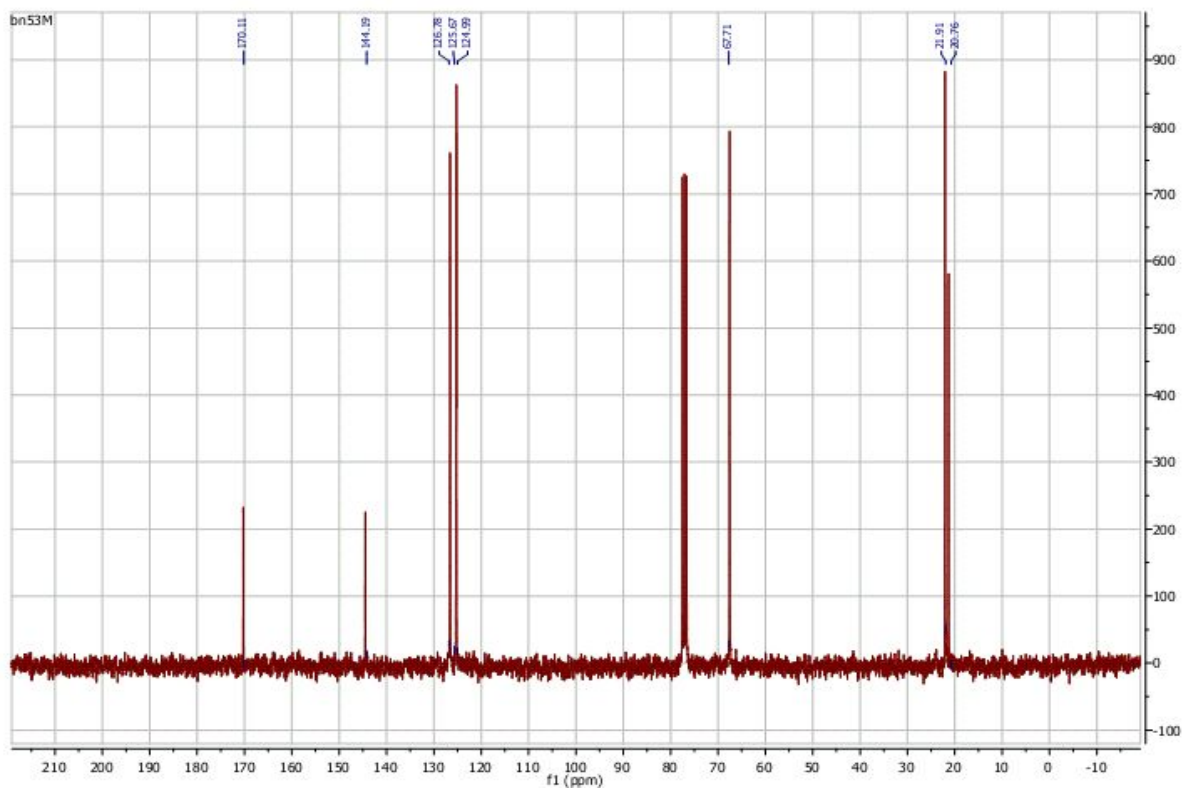
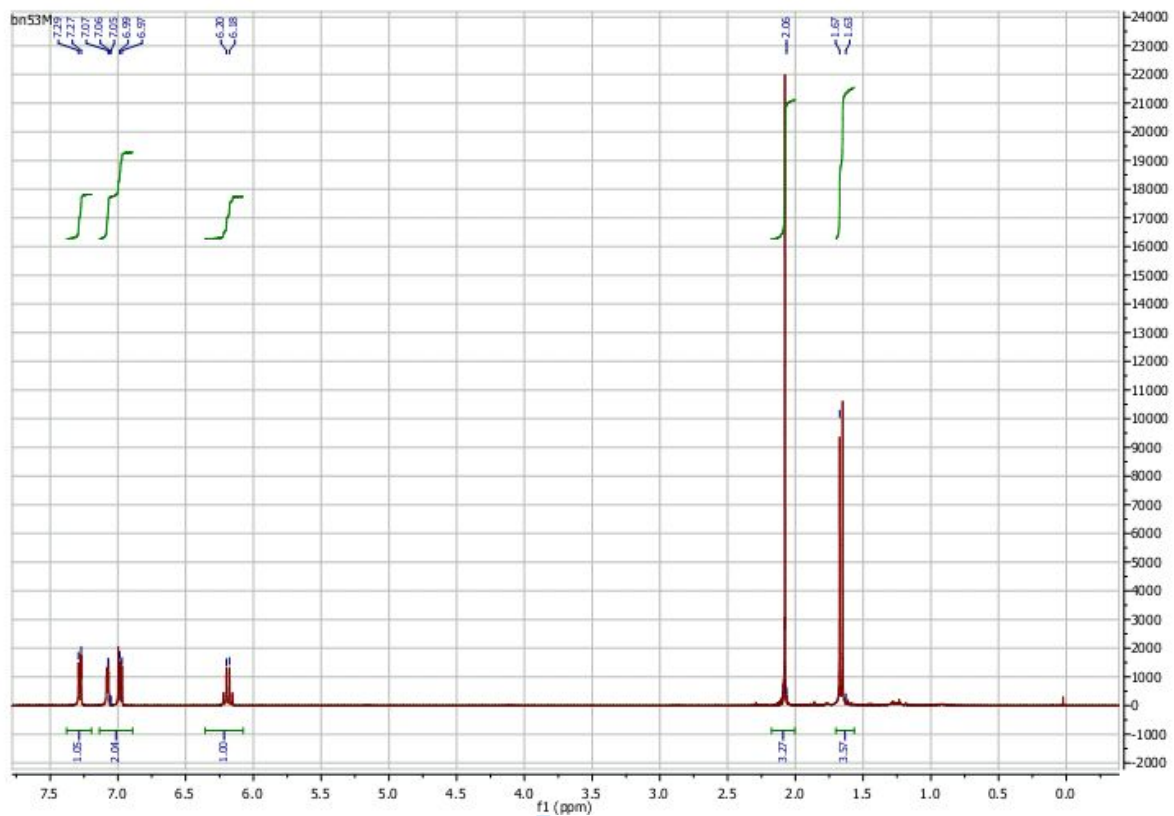


*Thiochroman-4-yl acetate (3a)*

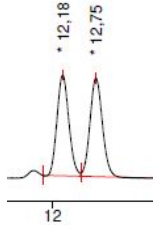
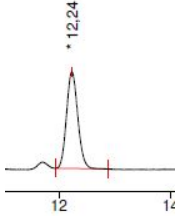
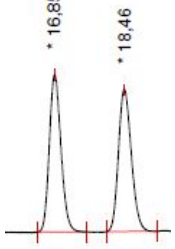
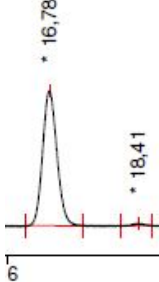


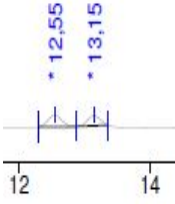
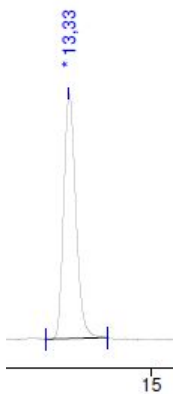
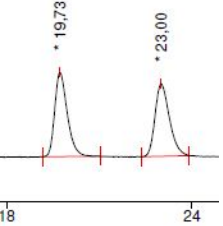

**1, 2, 3, 4-tetrahydronaphthalen-1-yl acetate (4a):**

*1-(fur-2-yl) ethyl acetate (5a)*

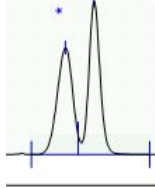


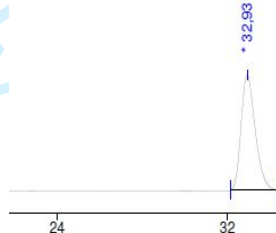
*1-(thien-2-yl)ethyl acetate (6a)*

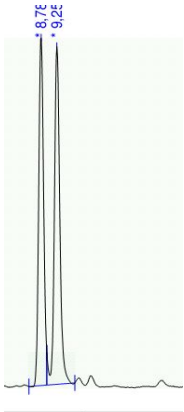

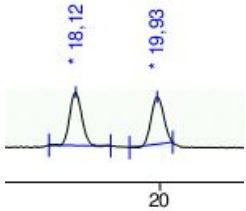
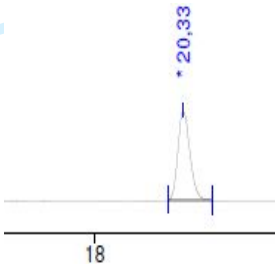
## 2. Chromatograms of some markedly results of the Alkaline-enzymatic hydrolysis

Substrate	Analysis's conditions	HPLC Chromatograms
<b>1a</b>	Chiral HPLC: <i>Chiralpak IA column</i> , $t_S = 12.18$ min, $t_R = 12.75$ min. Eluent (v,v): <i>n</i> -hexane/ <i>i</i> PrOH: 95/5; flow rate: 0.5 mL/min. ee > 99%. ( <i>S</i> )- <b>1a</b>	<p><b>Rac</b></p>  <p><b>(S)-1a</b></p> 
<b>1</b>	Chiral HPLC: <i>Chiralpak IA column</i> , $t_R = 16.85$ min, $t_S = 18.46$ min. Eluent (v,v): <i>n</i> -hexane/ <i>i</i> PrOH: 95/5; flow rate: 0.7 mL/min . ee > 99%. ( <i>R</i> )- <b>1</b>	<p><b>rac</b></p>  <p><b>(R)-1</b></p> 

<p><b>2a</b></p>	<p>Chiral HPLC: Chiralpak IA column, <math>t_R = 12.55</math> min, <math>t_S = 13.15</math> min. Eluent (v,v): n-hexane/EtOH: 99/1; flow rate: 0.5 mL/min.</p> <p>ee &gt; 99%. (<i>S</i>)-<b>2a</b></p> <p><math>[\alpha]_D^{20} = -182.6</math> (c 0.5, CHCl<sub>3</sub>).</p>	<p><i>rac</i></p>  <p><i>(S)</i>-<b>2a</b></p> 
<p><b>2</b></p>	<p>Chiral HPLC: Chiralpak ODH column, <math>t_S = 19.73</math> min, <math>t_R = 23.00</math> min. Eluent (v,v): n-hexane/iPrOH: 95/5; flow rate: 0.5mL/min.</p> <p>ee &gt;99% (<i>R</i>)-<b>2</b></p> <p><math>[\alpha]_D^{20} = +106</math> (c 0.5, CHCl<sub>3</sub>).</p> <p>[Lit<sup>1</sup>. (<i>R</i>)-<b>2b</b> <math>[\alpha]_D^{20} = +68</math> (c 0.36, CHCl<sub>3</sub>), 64%ee]</p>	<p><i>rac</i></p>  <p><i>(R)</i>-<b>2</b></p> 

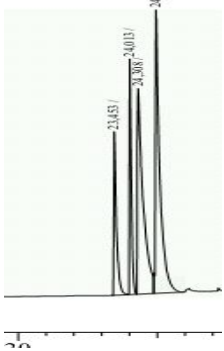

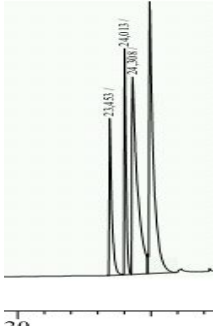
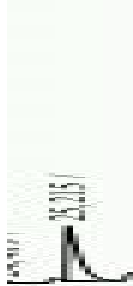
<sup>1</sup> Boyd D, Shama N.D, Boyle R, Evans TA, Malone JF, McCombe KM, Dalton H. *J Chem Soc Perkin* .1996;1:1758–1765.

<p><b>3a</b></p>	<p>Chiral HPLC: <i>Chiralpak</i> OD-H column, <math>t_R = 13.02</math> min, <math>t_S = 13.83</math> min. Eluent (v,v): n-hexane/iPrOH: 95/5; flow rate: 0.5mL/min.</p> <p><b>ee =98 %.</b> (<i>S</i>)-<b>3a</b></p> <p><math>[\alpha]_D^{20} = -213</math> (<i>c</i>0.5, CHCl<sub>3</sub>)</p>	<p><b>Rac</b></p>  <p><b>(S)-3a</b></p> 
<p><b>3</b></p>	<p>Chiral HPLC: <i>Chiralpak</i> OD-H column, <math>t_S = 25.15</math> min, <math>t_R = 31.65</math> min. Eluent (v,v): n-hexane/iPrOH: 95/5; flow rate: 0.5mL/min.</p> <p><b>ee &gt; 99%.</b> (<i>R</i>)-<b>3</b></p> <p><math>[\alpha]_D^{20} = +125</math> (<i>c</i>0.3, CHCl<sub>3</sub>).</p> <p>[Lit!. (<i>R</i>)-<b>3</b> <math>[\alpha]_D^{20} = +141</math> (<i>c</i> 2.11, CHCl<sub>3</sub>), &gt;97%ee]</p>	<p><b>Rac</b></p>  <p><b>(R)-3</b></p> 

<p><b>4a</b></p>	<p>Chiral HPLC: <i>Chiralpak IA</i> column, min, <math>t_R = 8.78</math> min, <math>t_S = 9.26</math>. Eluent (v,v): hexane/iPrOH: 95/5; flow rate: 0.5mL/min.</p> <p><b>ee = 85% (S)-4a</b></p> <p><math>[\alpha]_D^{20} = -71</math> (c 0.5, CH<sub>3</sub>Cl).</p> <p>[Lit.<sup>2</sup> (S)-4a: <math>[\alpha]_D^{20} = -97.5</math> (c 0.5, CHCl<sub>3</sub>), 90%ee]</p>	<p><b>rac</b></p>  <p><b>(S)-4a</b></p> 
<p><b>4</b></p>	<p>Chiral HPLC: <i>Chiralpak IA</i> column, <math>t_S = 18.12</math>min, <math>t_R = 19.93</math>min. Eluent (v,v): hexane/iPrOH: 95/5; flow rate: 0.5mL/min.</p> <p><b>ee &gt;99%. (R)-4</b></p> <p><math>[\alpha]_D^{20} = -29</math> (c0.3, CHCl<sub>3</sub>).</p> <p>[Lit.<sup>3</sup> (R)-4: <math>[\alpha]_D^{20} = -28</math> (c0.5, CHCl<sub>3</sub>), 99%ee]</p>	<p><b>rac</b></p>  <p><b>(R)-4</b></p> 

<sup>2</sup>Z. Houiene , M. Merabet-Khelassi , N. Bouzemi , Olivier Riant , L. Aribi-Zouieueche, Tetrahedron: Asymmetry (2013) 290–296, 828-833.



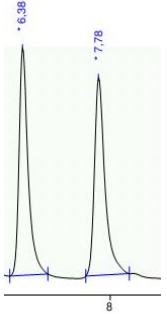
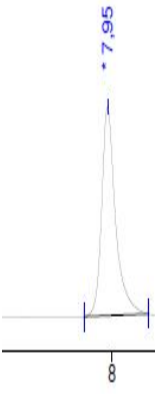
<sup>3</sup> Bouzemi, N.; Aribi-Zouieueche, L.; Fiaud, J. C. Tetrahedron Asymmetry 2006, 17, 797–800.

<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29</p> <p><b>5a</b></p>	<p>GC-2010 Plus: <i>Chiralpak</i> Shimadzu Chiraldex G-BP</p> <p>Gradient 60°C for 20 min; 10°C/min; 180°C for 20min</p> <p><math>t_S = 23.45</math> min, <math>t_R = 24.03</math>min.</p> <p><b>ee = 97%. (S)-5a</b></p> <p><math>[\alpha]_D^{20} = -129.2</math> (c 0.2, CHCl<sub>3</sub>).</p> <p>[Lit<sup>4</sup>. (R)-5a <math>[\alpha]_D^{20} = +145</math>(c 3.7, CHCl<sub>3</sub>), 99%ee]</p>	<p><i>rac</i></p>  <p>(S)-5a</p> 
<p>30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57</p> <p><b>5</b></p>	<p>GC-2010 Plus: <i>Chiralpak</i> Shimadzu Chiraldex G-BP</p> <p><math>t_S = 24.3</math> min, <math>t_R = 24.95</math> min. Eluent (v,v):acetone</p> <p><b>ee = 99%. (R)-5</b></p> <p><math>[\alpha]_D^{20} = +23.2</math> (c 0.1, CHCl<sub>3</sub>).</p> <p>[Lit<sup>5</sup>. (R)-5: <math>[\alpha]_D^{20} = +21</math> (c 1.45, CHCl<sub>3</sub>), 95%ee]</p>	<p><i>rac</i></p>  <p>(R)-5</p> 

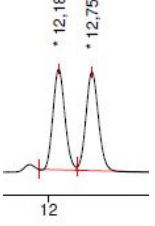
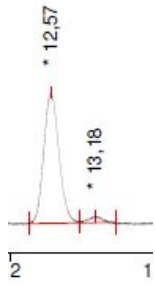
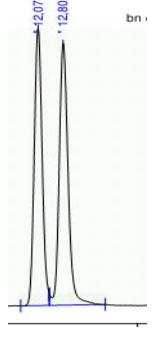
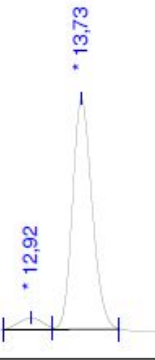
<sup>4</sup>Dartagnan S.P. Ferreira, Jeielly G. Ferreira, Everaldo F.S. Filhob, Jefferson L. Princivala. Journal of Molecular Catalysis B: Enzymatic 126 (2016) 37–45

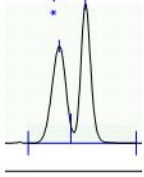
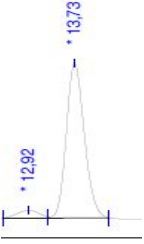
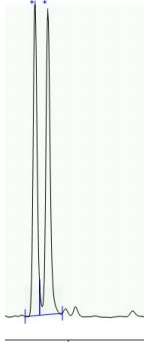
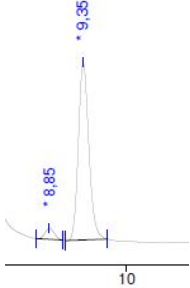
<sup>5</sup> Fantin G, Fogagnolo M, Medici A, Pedrini P, Polis S, Grdini F. Tetrahedron: Asymmetry.1993;4:1607–1612

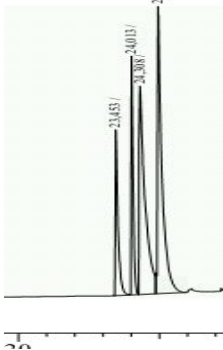

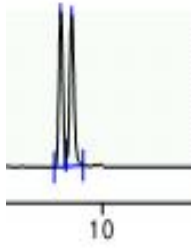


<p><b>6a</b></p>	<p>Chiral HPLC: <i>Chiralpak</i> IA column, <math>t_R = 8.38</math> min, <math>t_S = 8.80</math> min. Eluent (v,v): n-hexane/iPrOH: 95/5; flow rate: 0.5mL/min.</p> <p><b>ee &gt; 99%. (S)-6a</b></p> <p><math>[\alpha]_D^{20} = -69.7</math> (c 0.2, CHCl<sub>3</sub>).</p> <p>[Lit<sup>4</sup>. (R)-6a : <math>[\alpha]_D^{25} = +114</math>(c 5.15, CHCl<sub>3</sub>), &gt;99%ee]</p>	<p><i>rac</i></p>  <p>8.38</p> <p>8.80</p> <p>10</p> <p><b>(S)-6a</b></p>  <p>9.40</p>
<p><b>6</b></p>	<p>Chiral HPLC: <i>Chiralpak</i> Whelk column, <math>t_S = 6.38</math> min, <math>t_R = 7.78</math> min. Eluent (v,v): n-hexane/iPrOH: 75/25; flow rate: 0.7mL/min.</p> <p><b>ee &gt;99%. (R)-6</b></p> <p><math>[\alpha]_D^{20} = +29</math> (c 0.2, CHCl<sub>3</sub>).</p> <p>[Lit<sup>5</sup>. (R)-6: <math>[\alpha]_D^{25} = +27</math>(c 2.5, CHCl<sub>3</sub>), 96%ee]</p>	<p><i>rac</i></p>  <p>6.38</p> <p>7.78</p> <p>8</p> <p><b>(R)-6</b></p>  <p>7.95</p> <p>8</p>

## 3. Chromatograms of some markedly results after Mitsunobu esterification

Substrate	Analysis's conditions	HPLC Chromatograms
<p><b>1a</b></p>	<p>Chiral HPLC: <i>Chiralpak IA</i> column, <math>t_S = 12.18</math> min, <math>t_R = 12.75</math> min. Eluent (v,v): n-hexane/iPrOH: 95/5; flow rate: 0.5 mL/min.</p> <p><b>ee = 92%. (S)-1a</b></p> <p><math>[\alpha]_D^{20} = -30.7</math> (c 0.2, CHCl<sub>3</sub>).</p>	<p><i>rac</i></p>  <p><i>(S)-1a</i></p> 
<p><b>2a</b></p>	<p>Chiral HPLC: <i>Chiralpak IA</i> column, <math>t_R = 12.07</math> min, <math>t_S = 12.8</math> min. Eluent (v,v): n-hexane/EtOH: 99/01; flow rate: 0.5 mL/min</p> <p><b>ee = 89% (S)-2a</b></p>	<p><i>rac</i></p>  <p><i>(S)-2a</i></p> 

<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26</p> <p><b>3a</b></p>	<p>Chiral HPLC: <i>Chiralpak</i> OD-H column, <math>t_R =</math> 13.02 min, <math>t_S = 13.83</math> min. Eluent (v,v): n- hexane/iPrOH: 95/5; flow rate: 0.5mL/min <b>ee = 88% (S)-3a</b></p>	<p><b>rac</b></p>  <p><b>(S)-3a</b></p> 
<p>27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p><b>4a</b></p>	<p>Chiral HPLC: <i>Chiralpak</i> IA column, min, <math>t_R = 8.78</math> min, <math>t_S = 9.26</math>. Eluent (v,v): hexane/iPrOH: 95/05; flow rate: 0.5mL/min. <b>ee = 89.5% (S)-4a</b></p>	<p><b>rac</b></p>  <p><b>(S)-4a</b></p> 

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	<p><b>rac</b></p>  <p><b>(S)-5a</b></p> 
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	<p><b>rac</b></p>  <p><b>(S)-6a</b></p> 