UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Campus de São José do Rio Preto

Guilherme Silva Torrezan

Uso do glicerol, glicerol bruto da produção do biodiesel e outros solventes próticos na síntese de cetonas (E)-α,β-insaturadas

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Dissertação apresentada como parte dos requisitos para obtenção do título de Mestre em Química, junto ao Programa de Pós-Graduação em Química, do Instituto de Biociências, Letras e Ciências Exatas da Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de São José do Rio Preto.

Orientador: Prof. Dr. Luis Octavio Regasini

Co-orientador: Prof. Dr. Marcelo Freitas Lima

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Resumo

O glicerol é o principal co-produto da produção de biodiesel e vem sendo considerado como um solvente verde. Neste trabalho, utilizamos o glicerol e o glicerol bruto proveniente da produção de biodiesel para a síntese das cetonas α,β-insaturadas (*2E, 4E*) -1,5-difenilpenta-2,4-dien-1-ona (**1**) e (*2E, 6E*) -2,6-dibenzilidenociclohexanona (**2**), utilizando reações aldólicas mono- e dicondensadas, respectivamente. As cetonas **1** e **2** sintetizadas em glicerol e glicerol bruto forneceram rendimentos superiores aos outros solventes próticos, incluindo etanol, metanol, PEG-400 e água. Para investigar as razões que justificariam a eficiência do glicerol, foram realizados os cálculos computacionais usando a teoria do funcional da densidade, que validou o mecanismo E1cB, assim como uma barreira de energia de ativação que favorece a rota sintética usando o glicerol. Além disso, o glicerol bruto de óleo de milho e girassol foram utilizados na síntese de **1** e **2** durante quatro reciclos, demonstrando rendimentos finais de **59,0** e **48,2%**, respectivamente.

Palavras-chave: glicerol, solventes próticos, cetonas, Condensação aldólica, Biodiesel, Química Verde

Abstract

Glycerol is main co-product from biodiesel production and has been recognized as green solvent. Herein, we used glycerol and crude glycerol for synthesis of α,β-unsaturated ketones: (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (**1**) and (2*E*,6*E*)-2,6-dibenzylidenecyclohexanone (**2**), using mono- and dicondensation aldol reactions, respectively. Glycerol and crude glycerol were able to furnish **1** and **2** in yields higher than other protic solvents, including ethanol, methanol, PEG-400 and water. In order to investigate reasons for efficiency glycerol, we performed computational calculations using Density Functional Theory, which has validated E1cB mechanism, as well as favorable enegy barrier using glycerol. In addition, crude glycerol from corn and sunflower oils were used in synthesis of **1** and **2** for four recycles, displaying final yields of 59.0 and 48.2%, respectively.

Keywords: glycerol, protic solvents, ketones, Aldol condensation, Biodiesel ,Green chemistry

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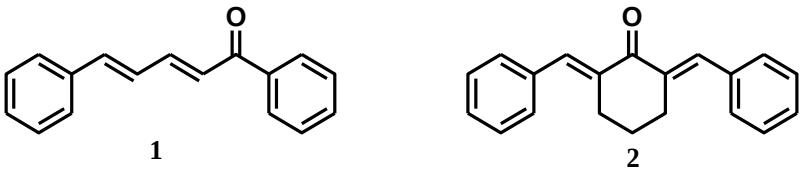
Sumário

INTRODUCTION

α,β-Unsaturated ketones are versatile structural subunits useful to heterocycle synthesis, due to reactivity of carbonyl and its behavior as Michael's acceptors, undergoing 1,2- and 1,4- nucleophilic additions, respectively (AGARWAL et al., 2009; MARZINZIK; FELDER, 1998; SAMSHUDDIN; NARAYANA; KUNHANNA, 2012). Furthermore, these ketones are present in bioactive natural and synthetic products. Among these, compounds containing (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (**1**) and (2*E*,6*E*)-2,6-dibenzylidenecyclohexanone (**2**) skeletons have demonstrated several bioactivities: antibacterial, antitubercular, antiviral, anti-cancer, and anti-helmintic (AGUILERA et al., 2016; GE et al., 2013; LAMBERT et al., 2013; MOHD FAUDZI et al., 2015; POLAQUINI et al., 2017; WEI et al., 2012; WELDON et al., 2014) (Figure 1).

Figure 1. Structures of ketones **1** and **2**



1 **2**

Aldol reactions have been extensively used for (*E*)-α,β-unsaturated ketones synthesis, which involves condensation between aldehydes and ketones, under acid or basis catalysis as well as protic solvents. Although, required use of solvents possess disadvantages, including flammability, low biodegrability and toxicity (MESTRES, 2004), the selection by suitable solvent is a crucial step for organic synthesis procedures. Several solvents has been developed, which are related to principles of green chemistry (or suitanable chemistry), including water, liquid ionics, polyethylenoglycol (PEG), perfluorinated solvents and glycerol (JESSOP, 2011; LENARDÃO et al., 2003).

Glycerol (or 1,2,3-propanetriol) is a versatile solvent and has been used in organic reactions due to several properties, including high boiling point, negligible vapor pressure, high polarity (able to solve organic and inorganic solutes), low-toxicity, high avaibility, biodegradability and biocompatibility (WOLFSON; DLUGY; SHOTLAND, 2007). It has been used in condensation reactions for synthesis of several compounds, including sulfanyl ketones (PERIN et al., 2014), *bis*(indolyl)methanes and *n*-

valeraldehyde (SILVEIRA et al., 2009; WOLFSON et al., 2009). Furthermore, glycerol has been studied as recyclable solvent by green procedures due to immiscibility in hydrophobic solvents, allowing removal of products by simple liquid-liquid extraction and successive reactions (PERIN et al., 2010; SILVEIRA et al., 2009).

Glycerol is the main co-product from transesterification reactions of acylglicerides from oils and fats (UMPIERRE; MACHADO, 2013). This reaction has been extensively used by biodiesel production, which displays rapid development, generating tremendous ammount of waste glycerol (million tons per year). Thus, reasonable solutions for utilization of waste glycerol are urgent topics from an environmental, social and economical point of view (QUISPE; CORONADO; CARVALHO JR., 2013; TAN; ABDUL AZIZ; AROUA, 2013).

Herein, we investigated effects of glycerol, crude glycerol from biodiesel production and other protic solvents, including ethanol, methanol, PEG-400 and water in synthesis of ketones **1** and **2**. Yields of aldol condensation reactions were calculated by gravimetry and chromatography measurements. In order to investigate comparisons between glycerol and water yields, theoretical investigations on mechanism of aldol condensation for synthesis of **1** were proposed using density functional theory calculations. In addition, crude glycerol from corn and sunflower oils were selected for re-use studies for synthesis of **1** and **2**, respectively.

2. EXPERIMENTAL

2.1. Materials and reagents

Cinnamaldehyde (99%), acetophenone (99%), benzaldehyde (99%), cyclohexanone (99%), PEG-400 (99%) and deuterated chloroform (99.8%) were purchased from Merck®. Methanol HPLC-grade (99.9%) was purchased from Merck®. Methanol (99.8%), ethanol (99.5%), glycerol (99.5%) and ethyl ether (98.0%) were purchased from Synth®. Water was distilled and purified through a MilliQ® apparatus. Soybean, corn, sunflower and castor oils used for synthesis of crude glycerol were bought in a supermarket.

2.2. Instrumentation and methods

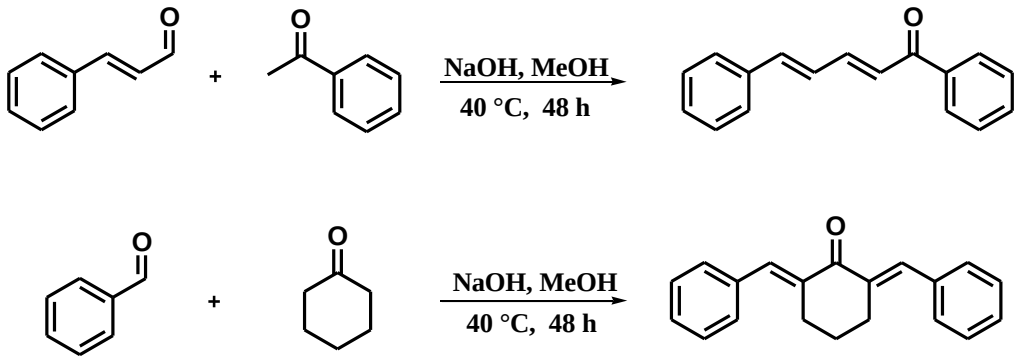
Nuclear Magnetic Resonance (NMR) spectra were recorded on two spectrometers: Bruker® Avance III 600 MHz (14.1 T) and Bruker® Fourier 300 MHz (7.1 T). Samples were dissolved in deuterated chloroform and its non-deuterated residue was used as internal standard for establishment of chemical shift values. NMR parameters, including chemical shifts (δ_H and δ_C in ppm), integrations, multiplicities and coupling constants (J in Hz) were measured. Low mass spectrometry by electrospray ionization (positive mode) spectra were performed on Bruker® Amazon ESI-IT. Peak attributed to protonated molecule $[M+H]^+$ were observed as base peak and selected to MS/MS experiments, which exhibited typical ions of α,β-unsaturated ketones fragmentation. Chromatography measurements were performed on system equipped with binary pump, automatic sampler column (Agilent Technologies® Model 1220 Infinity), photodiode array system (Agilent Technologies® Model 1260 Infinity) and mass spectrometry by electrospray ionization (positive mode) Agilent Technologies® Model 500-MS Ion Trap. Analyses were obtained at 344 and 328 nm for ketones **1** and **2**, respectively, and over C-18 Zorbax Eclipse Plus (4.6 × 250 mm, 5 μm, Agilent® Technologies) at 40 °C. Gradient elution with methanol and water was established as 75:25 (0 min), 95:5 (5 min), 95:5 (10 min) and 75: 25 (12 min). Collection and treatment of data were analyzed by software LC Solution Agilent Technologies®. Simultaneous thermogravimetry and differential scanning calorimetry (TG-DSC) curves were obtained in TG-DSC – 1 STARe system from Mettler Toledo®. The purge gas was dry air, flow

rate of 50 mL min^{-1}. A heating rate of 10 ºC min^{-1} was adopted, with samples (7 mg). Alumina crucibles were used for recording the TG-DSC curves.

2.3. Synthesis, identity and purity of reference samples of ketones 1 and 2

Ketones **1** and **2** are commercially unavailable. Reference samples of **1** and **2** were synthesized as previously described by Weldon and co-authors (2015) and Wei and co-authors (2012), respectively (figure 2) (WEI et al., 2012; WELDON et al., 2014). For synthesis of **1**, cinnamaldehyde (5 mmol) and acetophenone (5 mmol) were solubilized in methanol solution of NaOH (10 mL, 0.25 mol L^{-1}). For synthesis of **2**, benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were solubilized in methanol solution of NaOH (10 mL, 0.25 mol L^{-1}). For both synthesis, reaction media were stirred for 48 h at 40 °C and poured onto crushed ice from deionized water. Precipitate was filtered and purified by successive crystallizations in ethanol. Identity of ketones **1** and **2** was confirmed by spectroscopic techiniques, including ^{1}H and ^{13}C NMR and MS. NMR and MS spectra were shown in supplementary material. Purity of reference samples of ketones **1** and **2** was analysed by TG-DSC (Figure 2).

Figure 2. Synthesis of reference samples of ketones **1** and **2**



2.4. Synthesis of ketones 1 and 2 using glycerol and other protic solvents

Ketones **1** and **2** were synthesized using glycerol and other protic solvents, including ethanol, methanol, PEG-400 and water. Monocondensation aldol reaction for synthesis of **1**: mixture of cinnamaldehyde (5 mmol) and acetophenone (5 mmol) were solubilized in respective NaOH solution (10 mL, 0.25 mol L^{-1}). Dicondensation aldol

reaction for synthesis of **2**: mixture of benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were solubilized in respective NaOH solution (10 mL, 0.25 mol L^{-1}). For both condensations, reaction medium was stirred 40 °C. After 48 h, reaction media were poured onto crushed ice from deionized water (50 g), filtered, washed with cold deionized water (15 mL) and dried under reduced pressure for 48 h. Reactions were performed in three independent events. Qualitative analyses of crude products were established by ^{1}H NMR spectra experiments, identifying characteristic signals, mainly δ_H. Yields of reactions were determined by gravimetry and chromatography using HPLC-PAD. Chromatograms and NMR spectra were shown in supplementary material. For reference samples of ketones **1** and **2**, analytical curves were prepared using five concentrations, ranging from 5 to 1 ppm, in triplicate. Correlation coefficient (R^2) values from analytical curves of ketones **1** and **2** were 0.9990 and 0.9992, respectively. Quantitative determinations were made taking into account peak area at wavelength of maximum absorbance of ketones **1** and **2**. Values of chromatography yields were expressed in percentage.

2.5. Theoretical calculations

Aldol condensation reaction for synthesis of ketone **1** in glycerol and water were investigated using density functional theory calculations, in composite approach. Full geometry optimizations were performed on X3LYP functional (XU et al., 2012) and 6-31(+)G(d) basis set in solution using C-PCM implicit model for each interation (BARONE; COSSI, 2001; COSSI et al., 1996; TOMASI; MENNUCCI; CAMMI, 2005). Optimizations were followed by harmonic frequency calculations to obtain vibrational, rotational, and translational contributions to free energy. For optimized structures, single point energy calculations were performed using M11 functional (PEVERATI; TRUHLAR, 2011) with 6-311+(d,p) basis set also in solution via C-PCM, taking in account zero point energy for all species. M11 method was used to improve reliability of free energies, since X3LYP functional are less accurate. Standard condition of 1 mol L^{-1} was used for all reported thermodynamic data. All these calculations were performed using GAMESS v. 1 May 2013 (R1) program system (SCHMIDT et al., 1993). Proposed mechanism of aldol condensation reaction for synthesis of **1** was detailed in supplementary material.

2.6. Synthesis of ketones 1 and 2 using crude glycerol

Crude glycerol was obtained from transesterification (or alcoholysis) reaction according by Wolfson and co-authors, with minor modifications (WOLFSON et al., 2007). Crude glycerol was prepared by magnetic stirring 100 mL of respective oil (castor,corn, soybean and sunflower), 20 mL of methanol, 10 mL of ethanol with 2 g of potassium hydroxide. Reaction media were stirred for 10 minutes at 40 °C. Crude glycerol phase was separated from biodiesel phase using separating funnel.

Monocondesation aldol reaction for synthesis of **1**: mixture of cinnamaldehyde (5 mmol) and acetophenone (5 mmol) were solubilized in respective crude glycerol (10 mL). Dicondensation aldol reaction for synthesis of **2**: mixture of benzaldehyde (10 mmol) and cyclohexanone (5 mmol) were solubilized in respective crude glycerol (10 mL). For both condensations, reaction media were stirred 40 °C. After 48 h, reaction media were poured onto crushed ice from deionized water (50 g), filtered, washed with cold deionized water (15 mL) and dried under reduced pressure for 48 h. Reactions were performed in three independent events. Qualitative analyses of crude products were established by ^{1}H NMR spectra experiments, identifying characteristic signals, mainly δ_{H}. Chromatograms and ^{1}H NMR spectra were shown in supplementary material. Yields of reactions were determined by gravimetry and chromatography (HPLC-PAD).

Re-use of crude glycerol for synthesis of ketones **1** and **2** were performed as previously described by Radatz and co-authors, with minor modifications (RADATZ et al., 2011). In order to synthesize **1** and **2** were used crude glycerol from corn and sunflower oils, respectively. For continuous synthesis of **1**, cinnamaldehyde (1 mmol) and acetophenone (1 mmol) were solubilized in crude glycerol from corn oil. For continuous synthesis of **2**, benzaldehyde (2 mmol) and cyclohexanone (1 mmol) were solubilized in crude glycerol from sunflower oil. For both synthesis, reaction media were stirred at 40 °C. After 24 h, products were extracted by liquid-liquid partition with ethyl ether (3 × 15 mL). Upper phase was dried and solvent evaporated under reduced pressure for 48 h. Lower glycerol phase was reused directly for four recycles. Yields of reactions were determined by gravimetry and chromatography (HPLC-PAD). Chromatograms were shown in supplementary material.

3. RESULTS AND DISCUSSION

3.1. Synthesis, identity and purity of reference samples of ketones 1 and 2

Reference samples of ketones **1** and **2** were obtained as yellow cristals with yields of 60% and 70%, respectively. UV-Vis spectra of **1** and **2** indicated maximum absorption (λ_{max}) at 344 and 328 nm, corroborating presence of α,β,γ,δ-unsaturated ketone and α,β-unsaturated ketone systems, respectively. All NMR parameters of **1** and **2**, including chemical shifts (δ_H and δ_C), integrations, multiplicities and coupling contants (*J*), corresponded to proposed structures. The most resolved signals in ^{1}H NMR spectrum of **1** were doublet of doublets and doublet at δ_H 8.00 and δ_H 7.13 ppm, which were attributed to hydrogens H-2/H-6 and H-α, respectively. Doublet at δ_H 7.13 ppm demonstrated coupling constant value of 15.0 Hz, indicating configuration *E* for olefine between carbons α and β. The most caracteristic signal in the ^{1}H NMR spectrum of **2** was signal at δ_H 7.83 ppm, atributted to H-β. This signal exhibits triplet-like multiplicity, which is correlated to conformational restrictions caused by conjugated double bounds and six-membered ring. ^{13}C NMR spectra of **1** and **2** exhibited signal at δ_C 190.5 and 190.4 ppm, respectively, atributted to their carbonyl groups. Values of δ_C for these carbonyls are shifted to downfield due to conjugation with two double bonds.

Ketone 1. ^{1}H NMR (600 MHz): 8.00 (dd; *J* = 8.4 and 1.2 Hz; H-2 and H-6), 7.65–7.63 (H-β), 7.61–7.58 (H-4), 7.54–7.52 (H-3, H-5, H-2' and H-6'), 7.41–7.39 (H-3'and H-5'), 7.36–7.34 (H-4'), 7.13 (d; *J* = 15.0 Hz; H-α), 7.06–7.05 (H-γ and H-δ). **^{13}C NMR (150 MHz):** 190.5 (C=O), 144.9 (C-β), 142.0 (C-δ), 138.2 (C-1), 136.1 (C-1'), 132.7 (C-4), 129.2 (C-α), 128.9 (C-2 and C-6), 128.6 (C-3 and C-5), 128.4 (C-3' and C-5'), 127.3 (C-2' and C-6'), 126.9 (C-4') and 125.4 (C-γ).

Ketone 2: ^{1}H NMR (600 MHz): 7.83 (s; H-β), 7.50 (d; *J* = 7.6 Hz); H-2 and H-6), 7.44 (dd; *J* = 7.2 and 7.5 Hz; H-3 and H-5), 7.38–7.35 (H-4), 2.98–2.95 and 1.80–1.84 (methylenes of cyclohexanone ring). **^{13}C NMR (150 MHz):** 190.4 (C=O), 136.9 (C-8), 136.2 (C-1), 136.0 (C-β), 130.4 (C-3 and C-5), 128.6 (C-2 and C-6), 128.4 (C-4), 28.5 and 23.0 (methylenes of cyclohexanone ring).

MS spectra of **1** demonstrated peak at *m*/*z* 235, attributed to protonated molecule $[M+H]^+$, and was selected to MS/MS experiments. Base peak at *m*/*z* 217 was related to neutral elimination of water from protonated molecule $[M+H–H_2O]^+$. Peak at *m*/*z* 105

was related to benzoyl cation $[PhCO]^+$. MS spectra of **2** demonstrated peaks at *m*/*z* 275, 297 and 313, attributed to $[M+H]^+$, $[M+Na]^+$ and $[M+K]^+$ ion, respectively. MS/MS experiments of protonated molecule indicated of tropylium ion at *m*/*z* 257.

Purity of reference samples of ketones **1** and **2** were analyzed by melting process, indicating their melting points (T_0) and enthalpies of fusion ($\Delta H_{fus.}$) values (Figure 3). Effect of impurities on T_o values was determined by DSC based on Van't Hoff equation (CAMPOS et al., 2014; TEIXEIRA; SIQUEIRA, 2016). DSC curves exhibited endothermic event at 103 °C (ΔH_{fus}= +25.36 kJ mol^{-1}) and 119 °C (ΔH_{fus}= +28.43 kJ mol^{-1}), corresponded to melting points of **1** and **2**, respectively. Purity of **1** and **2** was found to be 99.66% and 99.35%, respectively. TG-DSC curves in dynamic dry air indicated ketones **1** and **2** were stable up to 155 °C and 207 °C, respectively. Thermal decomposition of **1** and **2** were observed in two and three steps, between 155 – 670 °C and 207 – 612 °C, with total mass loss of 99.12 % and 100.00 %, respectively. These percentages indicated reference samples of ketones **1** and **2** did not contain inorganic impurities.

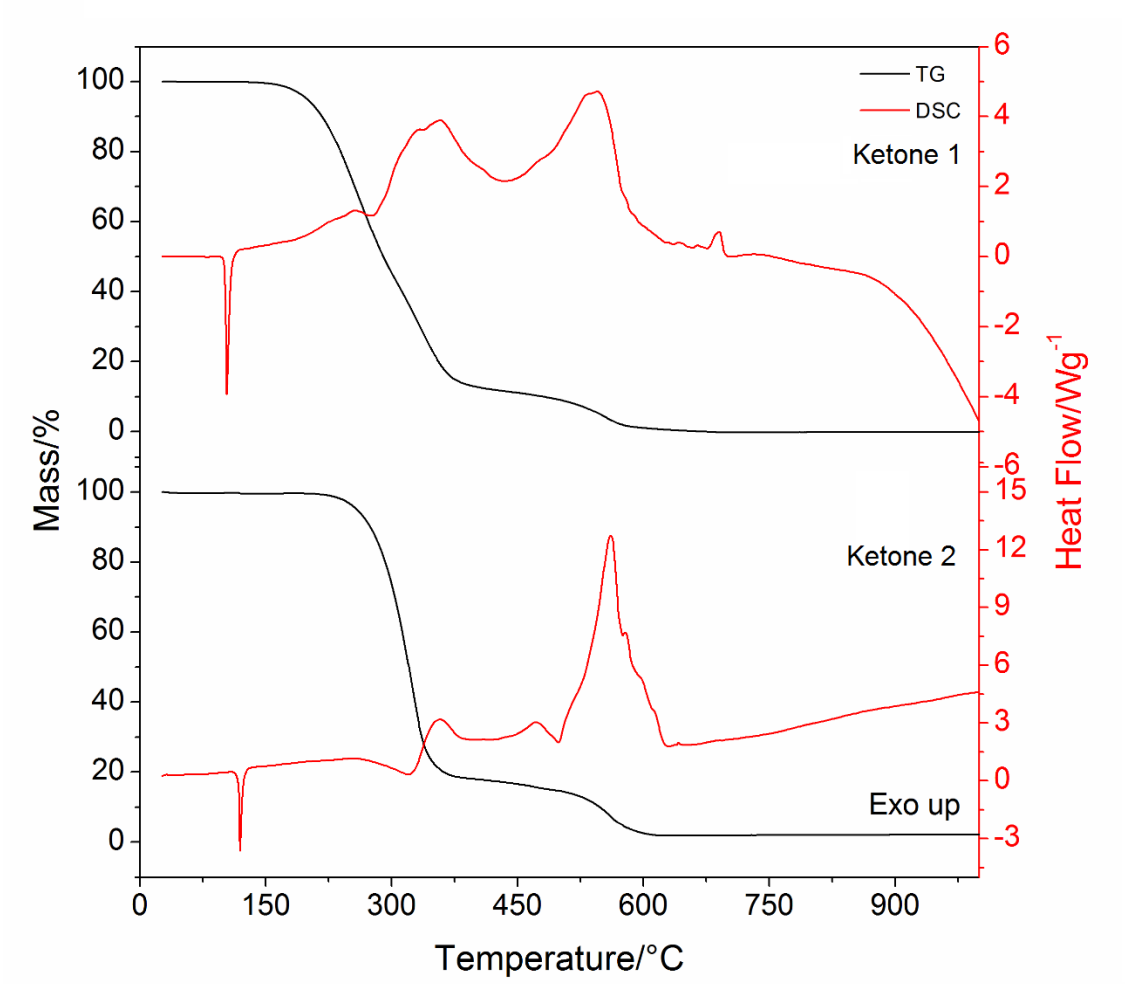
TG-DSC curves of **1** showed first mass loss occurs in slowly process, with mass loss of 88.05 % between 155 and 419 °C, associated to exothermic peak at 255 °C and to exotherm between 277–428 °C in DSC curve. This event was attributed to thermal decomposition and/or oxidative degradation. DSC curve of **1** indicated small exothermic peak at 255 °C in relation to large mass loss observed in TG curve. This event was attributed to oxidation of carbonaceous residue (exo) and thermal decomposition of material (endo), because produced heat was not sufficient to cause large thermal event (TEIXEIRA et al., 2016). Two last of mass loss occurred between 428–580 °C and 580–670 °C indicated by exotherm between 432–585 °C and exothermic events between 628–700 °C, repectively. These phenomena were attributed to oxidative degradation of carbonaceous residue produced in previous step, with mass loss of 12.03%.

TG-DSC curves of ketone **2** demonstrated first and fast mass loss between 207 and 382 °C, with mass loss of 80.99 %. In this step, DSC curve exhibited endothermic (322 °C) and exothermic (355 °C) events, attributed to thermal decomposition and/or oxidative degradation, respectively. In the second stage of thermal decomposition, two overlapping steps between 382–612 °C, with reduction of 18.13 %, were associated to exothermic peak at 469 °C and a large exothermic event on the DSC curve between 501–

629 °C. These phenomena were attributed to oxidation of carbonaceous residue produced in previous step and/or gaseous products, which involved thermal decomposition and oxidation.

For both reference samples, carbonaceous residue was confirmed by visual inspection, heating samples up to 419 ºC and 382 °C for ketones **1** and **2**, as indicated by TG-DSC curves, respectively.

Figure 3. Simultaneous TG-DSC curves in dynamic dry air atmosphere of reference samples of ketones **1** and **2**



3.2. Synthesis of ketones 1 and 2 using glycerol and other protic solvents

Table 1 summarized gravimetry and chromatography yields of synthesis of ketones **1** and **2** using glycerol and other protic solvents. Gravimetry measurements for

ketone **1** synthesis indicated following order of yields: PEG-400 > glycerol > ethanol > methanol > water. In general, alcohol with long side chain lead to higher yields than short side chain alcohols. In contrast to gravimetry, chromatography yields indicated PEG-400 and ethanol were completly inefficient in synthesis of **1**. In order to support this result, ^{1}H NMR of **1** synthesized in PEG-400 and ethanol did not exhibit characteristic signals of ketone **1**.

Table 1. Gravimetry and chromatography yields of synthesis of ketones **1** and **2** in glycerol and other protic solvents

	ketone **1**		ketone **2**	
Protic Solvent	Gravimetry Yield (%)	Chromatography Yield (%)	Gravimetry Yield (%)	Chromatography Yield (%)
glycerol	86	92.5	87	84.2
ethanol	80	nd	84	92.5
methanol	68	36.5	82	94.0
PEG-400	120	nd	89	67.7
water	37	64.0	87	8.5

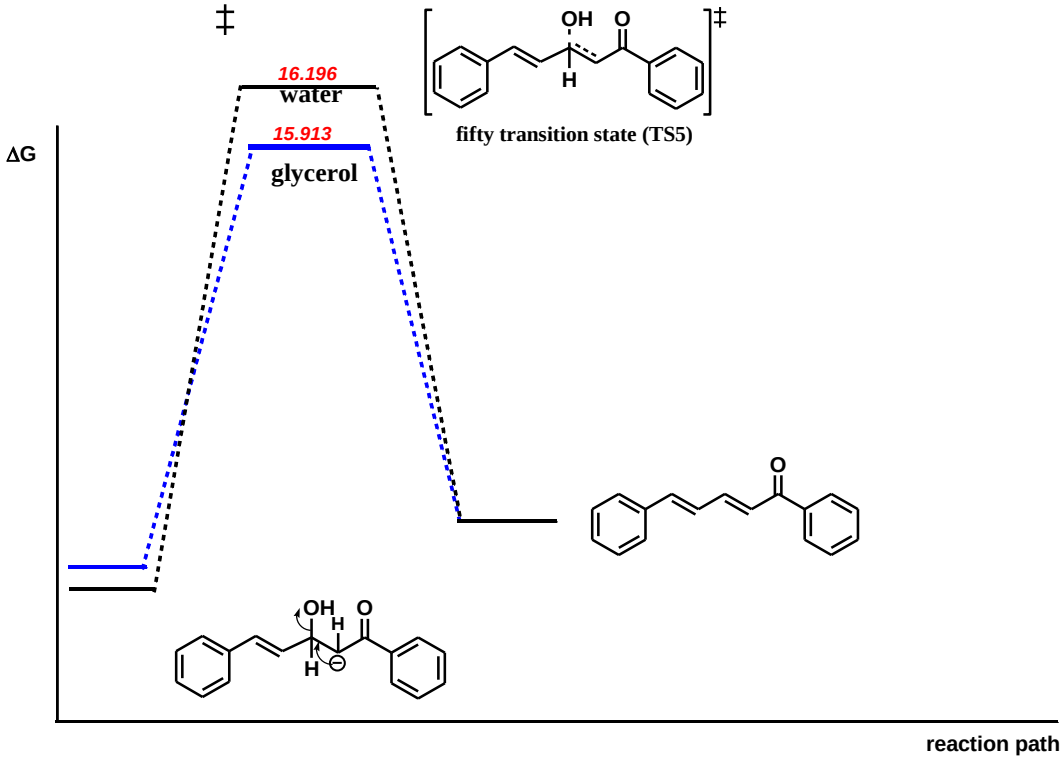
nd = not detectable

Glycerol and water were the two most efficient solvents for synthesis of **1**, exhibiting yields of 92.5 and 64.0%, respectively. Gu and Gerome have exhaustively revised similar properties of glycerol in comparison to water, including low toxicity, low price and large avaibility (GU; JÉRÔME, 2010). Thus, we purposed theoretical studies on mechanism of reaction for synthesis of ketone **1** in water and glycerol, using DFT calculations (geometry and energy with implicit C-PCM solvation effect included in each interaction). We have found no evidence for concerted bimolecular elimination (E2) route. However, conjugated base (carbanion, E1cB) was confirmed by calculation of second derivative of wavefunction. Furthermore to intrinsic reaction coordination path,

each transition state lead to E1cB. Among these, determining step was the cleavage of bonding C–OH, and release of hydroxide. These data corroborated studies described by Perrin and Kuei-Lin Chang (PERRIN; CHANG, 2016). Perrin and Chang, suggested the **1** highest-energy transition state of synthesis of α,β-unsaturated ketones is for release of

hydroxide as leaving group (last transition state). For ketone **1,** synthesis in water and glycerol, energy calculations of second derivative of molecular orbitals were performed to generate free energy of activated complexes. Figure 4 summarized free energy diagram corresponding to determining step of reaction (fifth transition state TS5) (supplementary materials) via E1cB mechanism. DFT calculations indicated glycerol was slightly more efficient ($\Delta G^{\ddagger}$ = 15.913 kcal mol^{-1}) than water ($\Delta G^{\ddagger}$ = 16.196 kcal mol^{-1}) to reduce energy of transition state at determining step of aldol condensation. This result confirms preferable kinetic control on the more favorable route for glycerol, but more important than that, it proves that glycerol (ΔG_{solv} (TS5) = –78.83 kcal mol^{-1}) can substitute water as a preferable solvent, once it can stabilize electronic density of transition state, as well as water (ΔG_{solv} (TS5) = –79.74 kcal mol^{-1}) and overcome solvation issues of water regarding its high polarity. Inversion of carbanion stabilization by water and glycerol, Energy of solvation in water is higher than in glycerol, –66.01 kcal mol^{-1} and –64.99 kcal mol^{-1}, respectively. This inversion contributes to increase of activation energy of TS5 in water. Theoretical results are according to chromatography yields of ketone **1** and contribute to use of glycerol as a green solvent, with similar suitainabity to water.

Figure 4. Free energy (kcal mol $^{-1}$) of determining step of synthesis of ketone **1** via E1cB mechanism in water and glycerol



Gravimetry yields of glycerol and other protic solvents for synthesis of ketone **2** were closely similar, ranging from 82 to 87%. On the other hand, chromatography measurements indicated high yields for synthesis in glycerol, ethanol and methanol (84.2–92.5%). Interestingly, water was not good media to synthesis of ketone **2** (8.5%), when compared to synthesis of ketone **1**. This low yield can be related to high ratio of polarity balance between solvent and structures involved in ketone **2** mechanism. Furthermore highly hydrophobic properties of reactants causes difficulting solute-solvent interactions. However, water was efficient for synthesis of ketone **1**. We hypothesized difference between mono- and dicondensation reactions can be explained based on stoichiometric ratio. For syntheses of **1** and **2** were used ratio between ketone and aldehyde of 1:1 and 1:2 (Scheme 1), respectively. Thus, reaction medium for synthesis of **2** was more concentrated than reaction medium for synthesis of **1**, which did not allow good solubility of reactants.

3.3. Synthesis of ketones 1 and 2 using crude glycerol

Use of crude glycerol from biodiesel production was investigated as reaction medium, using several oil sources: castor, corn, soybean and sunflower. As KOH from catalyzed oil transesterification is also left in crude glycerol phase (Wolfson et al., 2009), synthesis of ketones **1** and **2** were performed without addition of KOH. Table 2 indicated gravimetry and chromatography yields of synthesis of ketones **1** and **2** using crude glycerol from oil sources.

Table 2. Gravimetry and chromatography yields of synthesis of ketones **1**, **2** and **2.a** in crude glycerol from oils

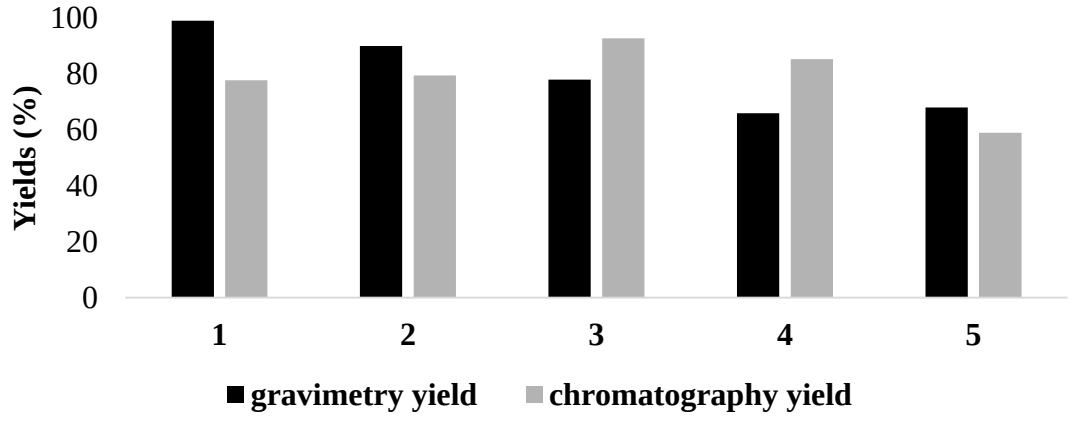
Source of Crude Glycerol	ketone **1**		ketone **2**		ketone **2.a**
	Gravimetry Yield (%)	Chromatography Yield (%)	Gravimetry Yield (%)	Chromatography Yield (%)	Chromatography Yield (%)*
castor	82	82.0	90	62.7	25.3
corn	88	92.5	93	59.0	28.2
soybean	81	87.5	87	51.5	37.8
sunflower	95	81.0	89	64.2	24.3

As expected, crude glycerol from all vegetable oils were good reaction media for mono- and dicondensation reactions. For synthesis of **1** and **2**, gravimetric yields ranging from 81 to 95%. Moreover, oil source did not affect reaction performance. However, chromatography yields of monocondensation were higher than those dicondensation. These data corroborated yields of synthesis of **1** and **2** in commercial glycerol (Table 1). Among tested crude glycerol, transesterification of corn and sunflower oils were the two most efficient, demonstrating chromatography yields of 92.5 and 64.2% for synthesis of **1** and **2**, respectively. Synthesis of ketone **2** produced by-product **2.a** (Supplementary Materials). UV-vis spectrum of **2.a** indicated λ_{max} at 322 nm, closely similar to λ_{max} of ketone **2** (328 nm). In addition, HPLC-MS analysis of **2.a** (*tr* ~ 7.3 min) and **2** (*tr* ~ 7.9 min) demonstrated peaks at *m/z* 275 (base peak) and *m/z* 297, attributed to $[M+H]^+$ and $[M+Na]^+$ ions. Ketone **2** and its by-product **2.a** demonstrated similar λ_{max} and identical mass molecular, suggesting both are geometric isomers. Table 2 indicated chromatography yields of ketone **2.a**. High yields of ketone **2.a** in crude glycerol from corn and soybean oils was correlated to low yields of ketone **2**.

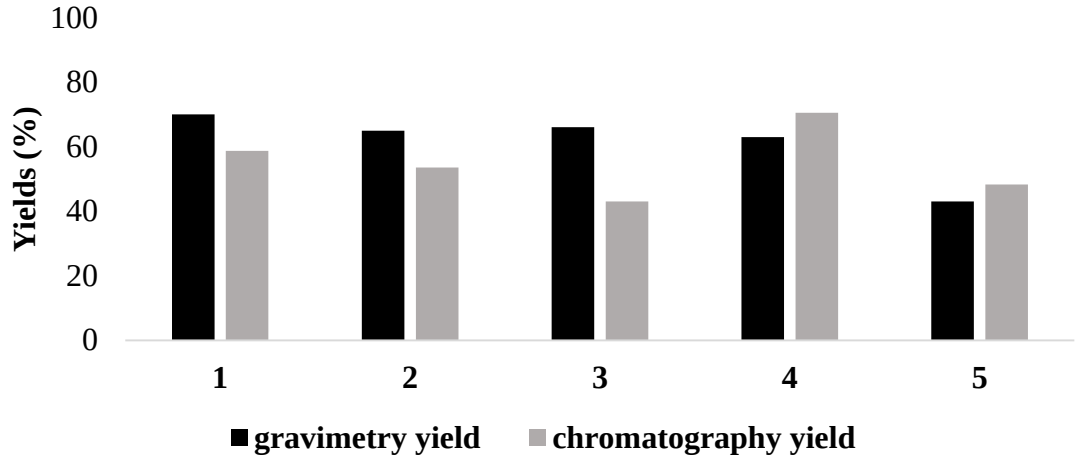
Crude glycerol from corn and sunflower oils exhibited the highest chromatography yields and were selected as reaction medium for re-use investigations in synthesis of **1** and **2,** respectively. Gravimetry and chromatography yields were presented in Figures 5a and 5b.

Figure 5. Gravimetry and Chromatography yields of re-use investigations

a) Re-use of crude glycerol from corn oil



b) Re-use of crude glycerol from sunflower oil



In both experiments, crude glycerol demonstrated good level of efficiency, which was maintained even aften being reused four times. Gravimetry yields for synthesis of ketones **1** and **2** decreased cycle-by-cycle, whereas chromatography measurements indicated maximum yields at third and fourth cycles, respectively. After four runs, ketones **1** and **2** were obtained in chromatography yields of 59.0 and 48.2%, respectively.

4. CONCLUSION

In conclusion, glycerol and crude glycerol from biodiesel production have proved to be an efficient and ecologically preferable reaction medium for synthesis of α,β-unsaturated ketones **1** and **2,** complying with the requirements of green chemistry, such as safe synthesis and the use of source renewable raw materials. Gravimetry and chromatography yields in glycerol and crude glycerol were higher than other protic solvents, including ethanol, methanol, PEG-400 and water. Theoretical investigations were able to suggest the mechanism of aldol reaction as E1cB, as well as make a detailed energetic comparison between glycerol and water role as a solvent on determining step of reactions. In addition, crude glycerol from corn and sunflower oils can be easily recovered and used for further mono- and dicondensation reactions and is notably relevant to green chemistry concept.

5. AKNOWLEDGMENTS

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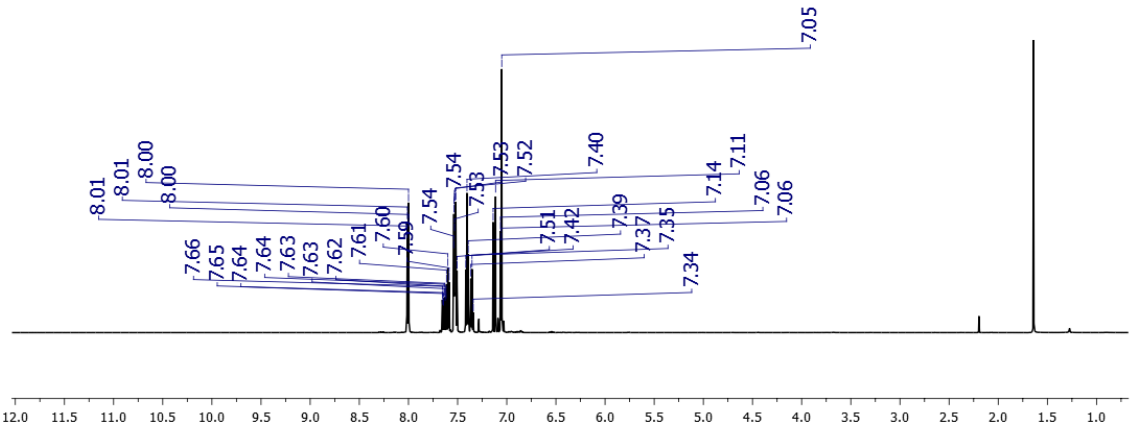
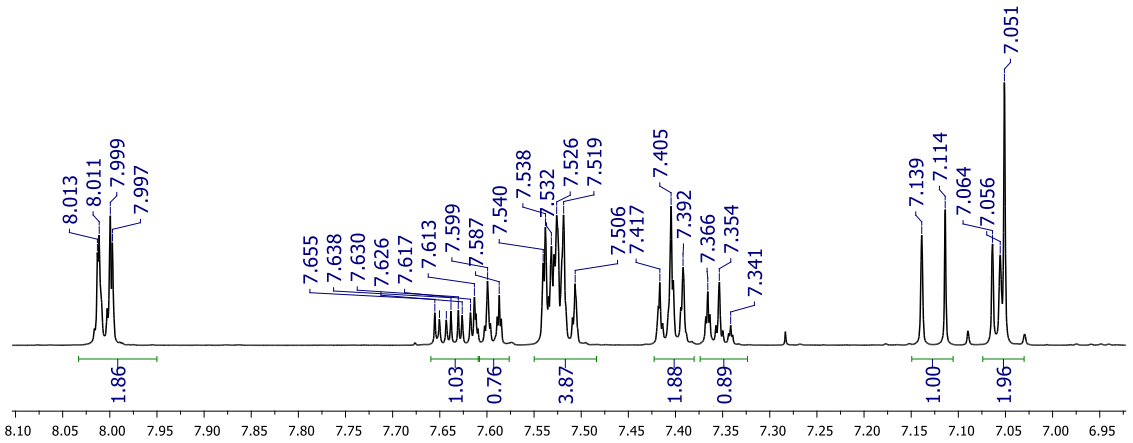
SUPLEMENTARY MATERIALS

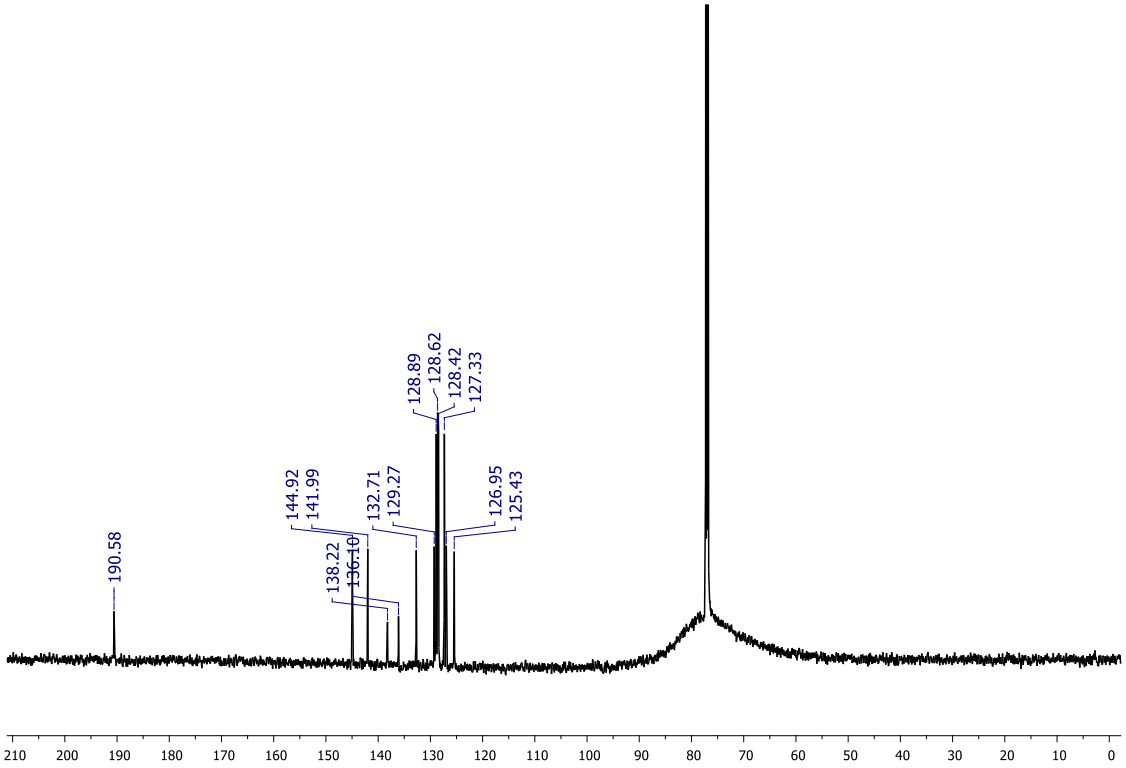
Anexo 1. ^{1}H NMR Spectrum of reference sample of ketone **1** ($CDCl_3$; 600 MHz)



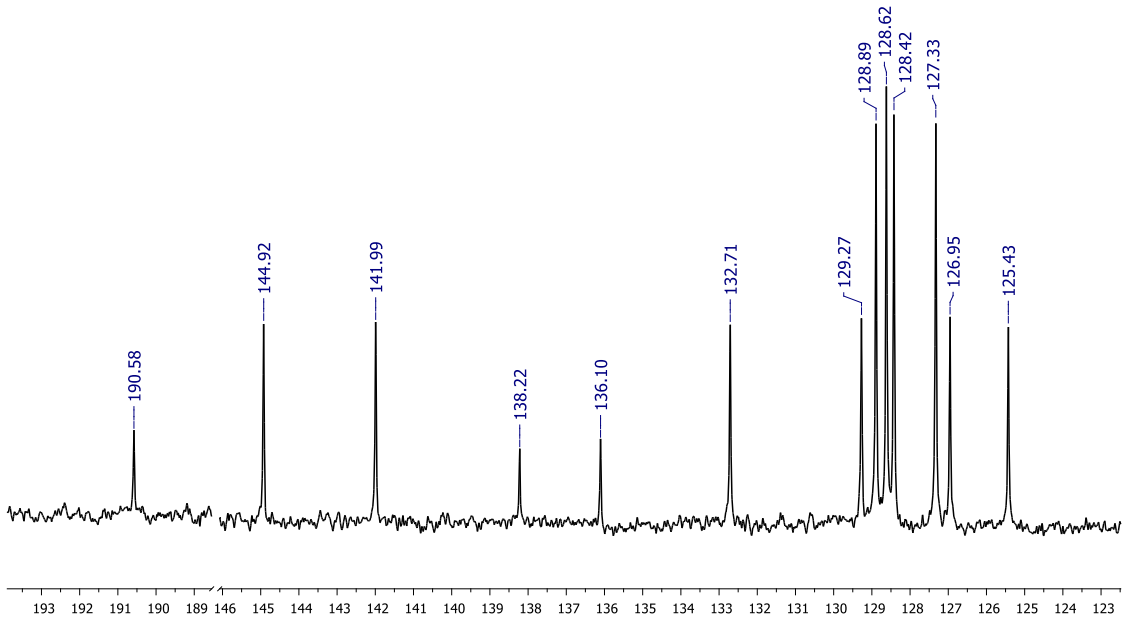
Anexo 2.. Expansion of ^{1}H NMR spectrum of reference sample of ketone **1** ($CDCl_3$; 600 MHz)



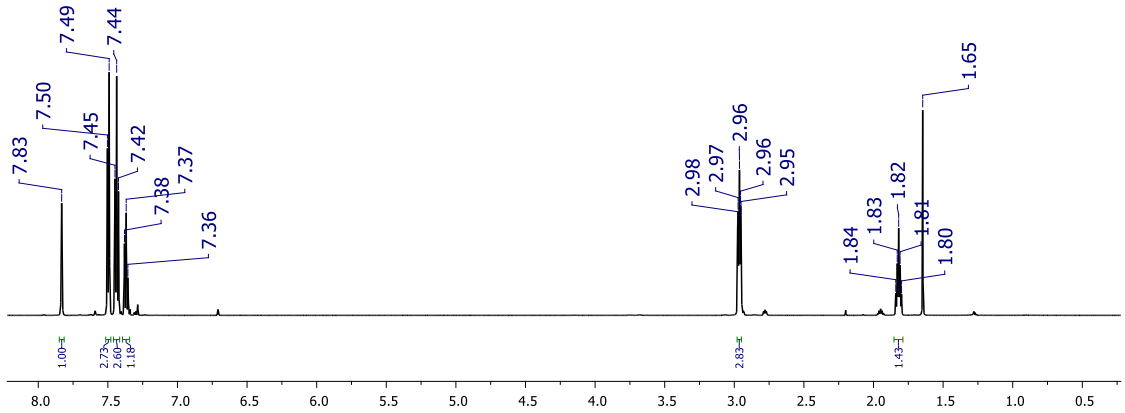
Anexo 3. ^{13}C NMR spectrum of reference sample of ketone **1** ($CDCl_3$; 150 MHz)



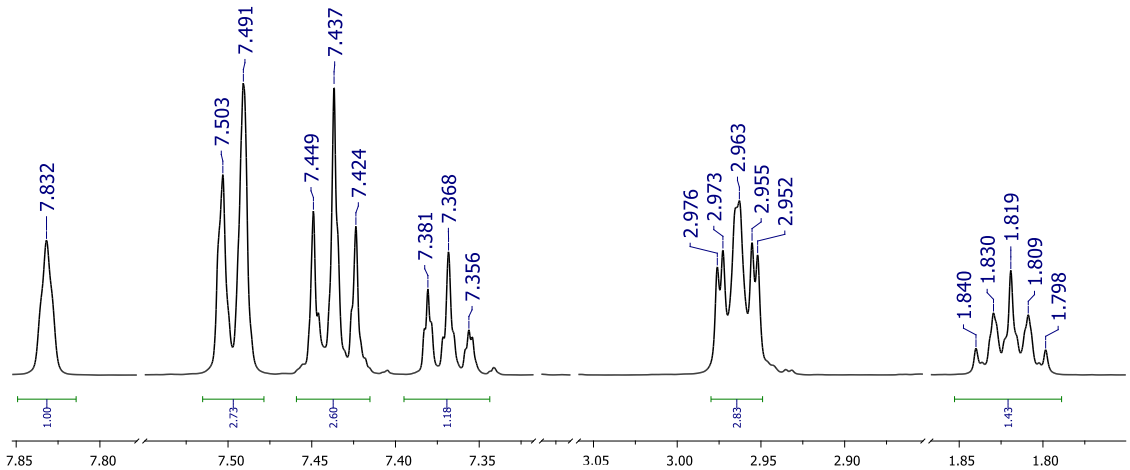
Anexo 4. Expansion of ^{13}C NMR spectrum of reference sample of ketone **1** ($CDCl_3$; 150 MHz)



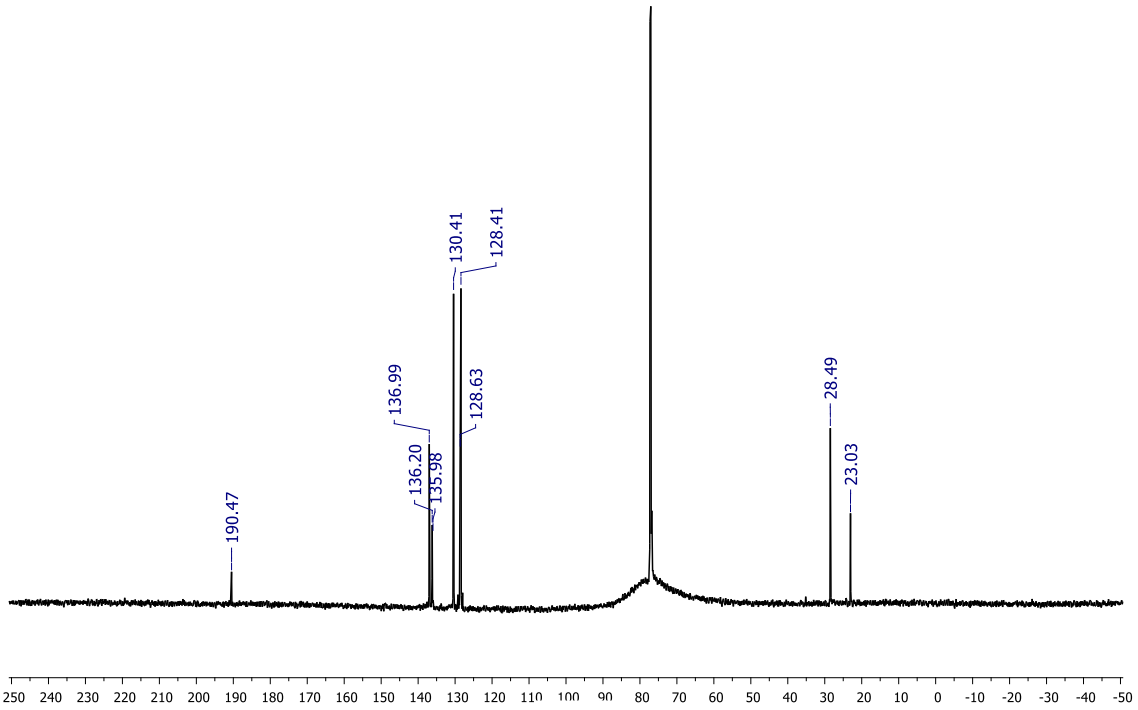
Anexo 5. ^{1}H NMR spectrum of reference sample of ketone **2** ($CDCl_3$; 600 MHz)



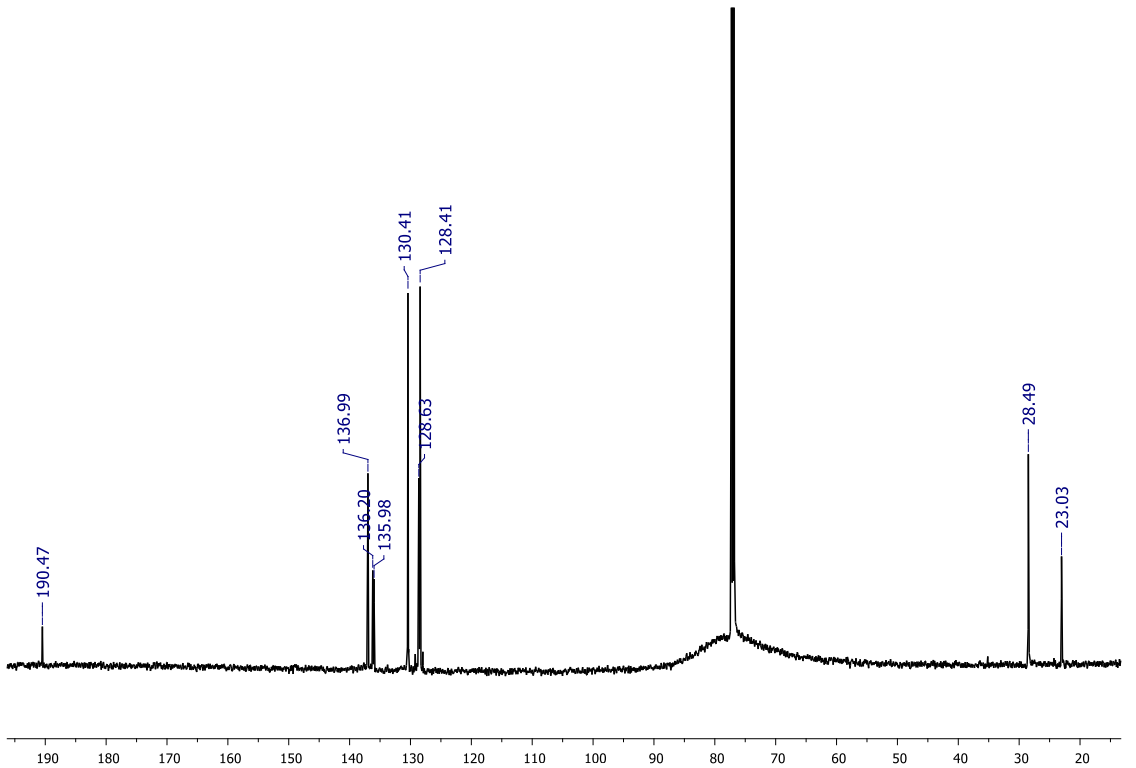
Anexo 6. Expansion of ^{1}H NMR spectrum of reference sample of ketone **2** ($CDCl_3$; 600 MHz)



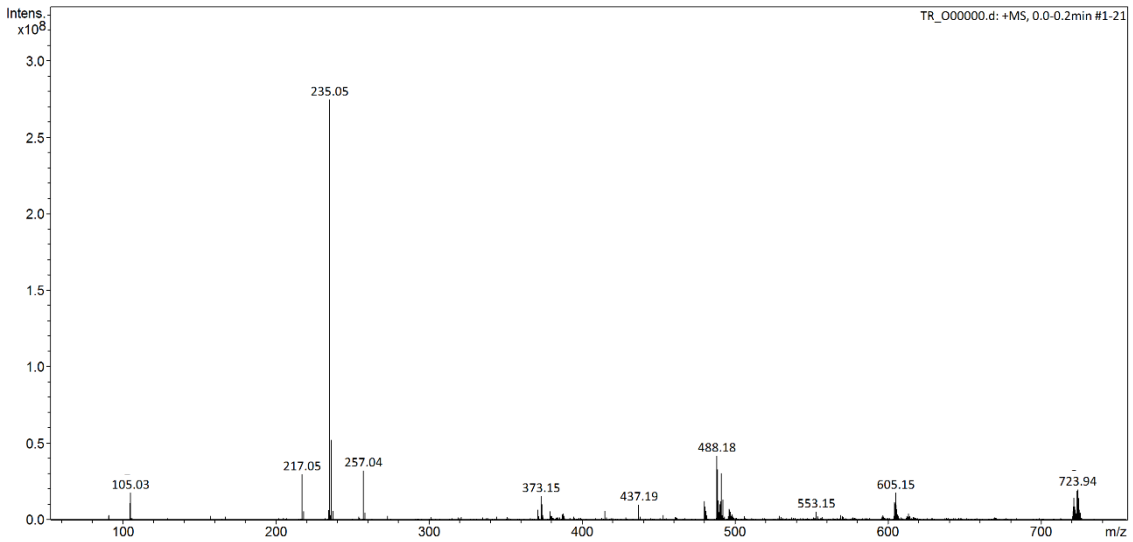
Anexo 7. ^{13}C NMR spectrum of reference sample of ketone **2** ($CDCl_3$; 150 MHz)



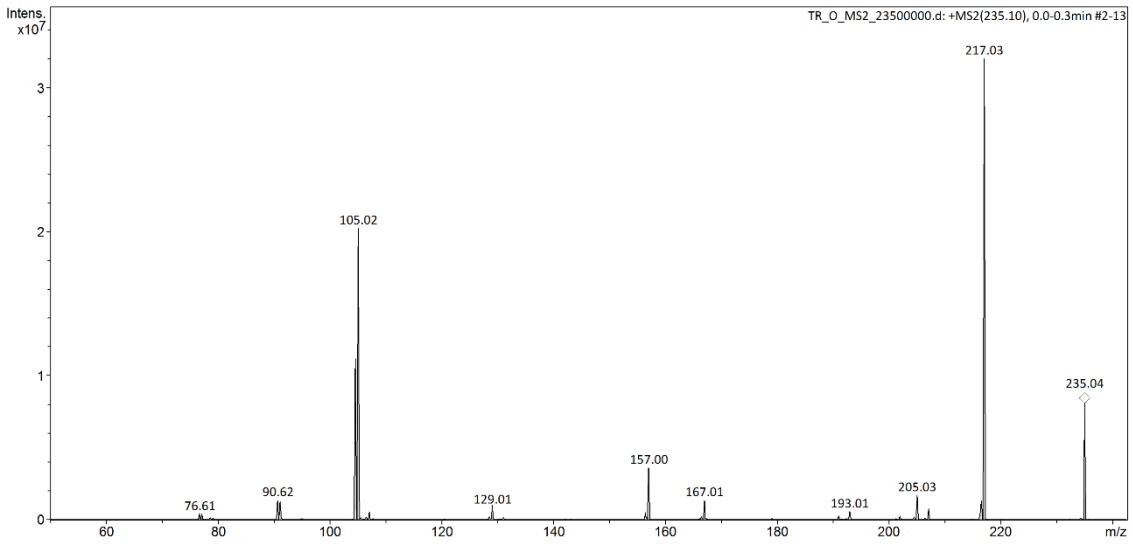
Anexo 8. Expansion of ^{13}C NMR spectrum of reference sample of ketone **2** ($CDCl_3$; 150 MHz)



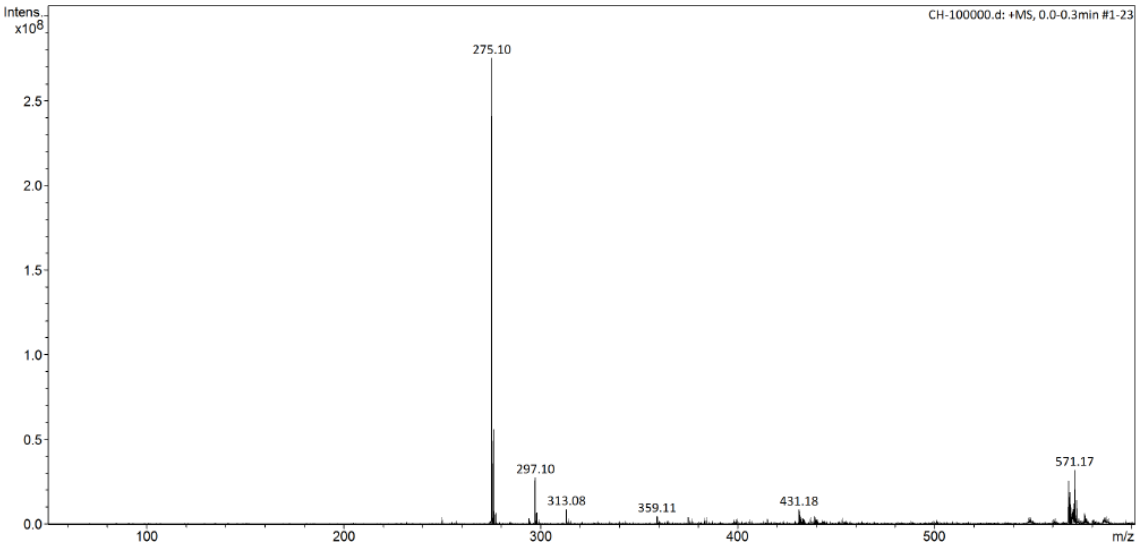
Anexo 9. Mass spectrum (MS) of reference sample of ketone **1**.



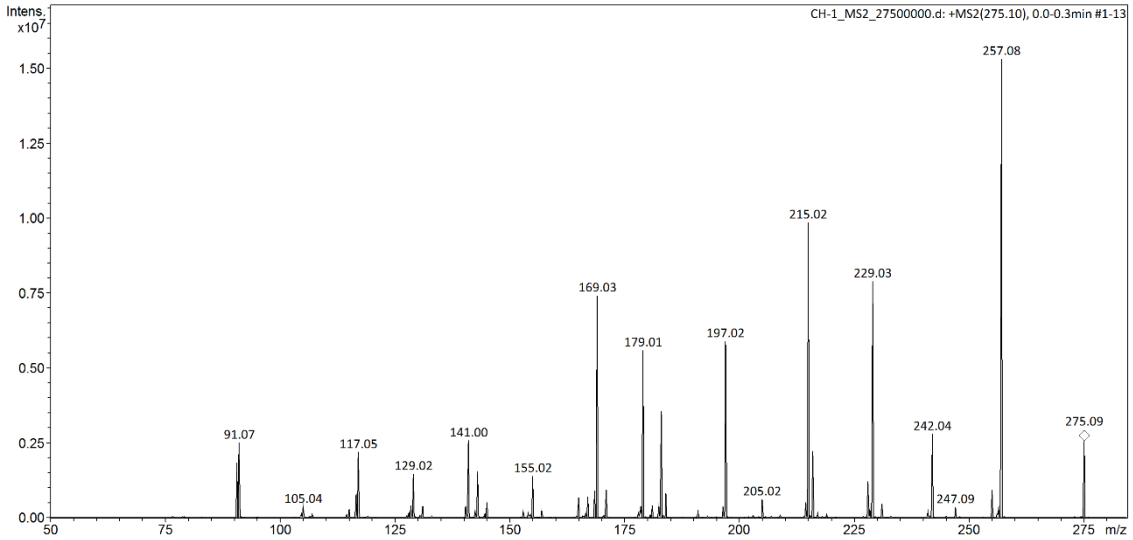
Anexo 10. Mass spectrum (MS/MS), precursor ion *m/z* 235.04 $[M + H]^+$ of reference sample of ketone **1**



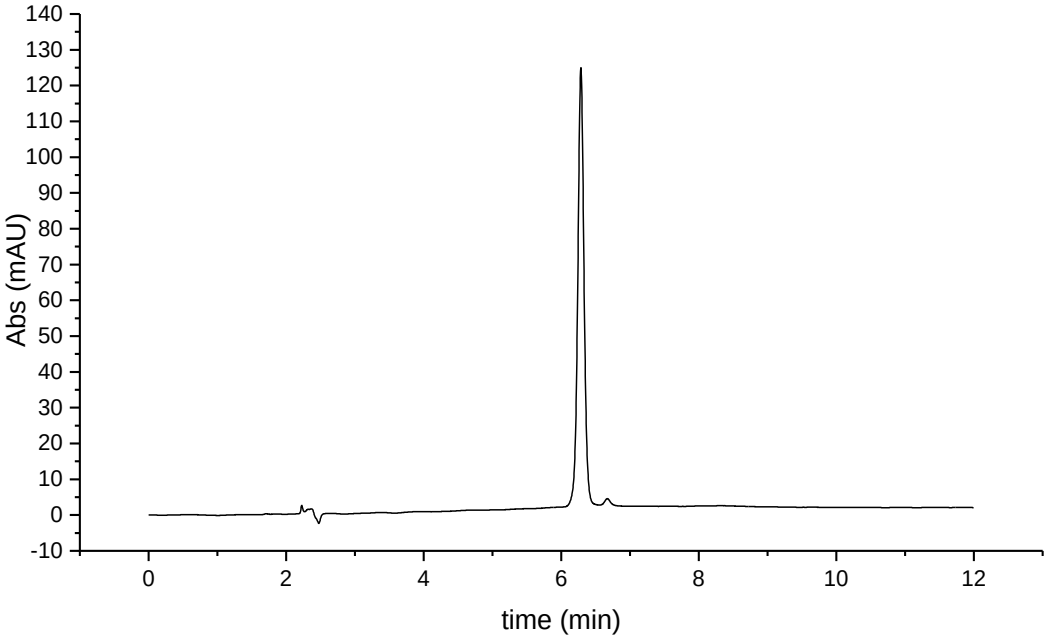
Anexo 11. Mass spectrum (MS) of reference sample of ketone **2**



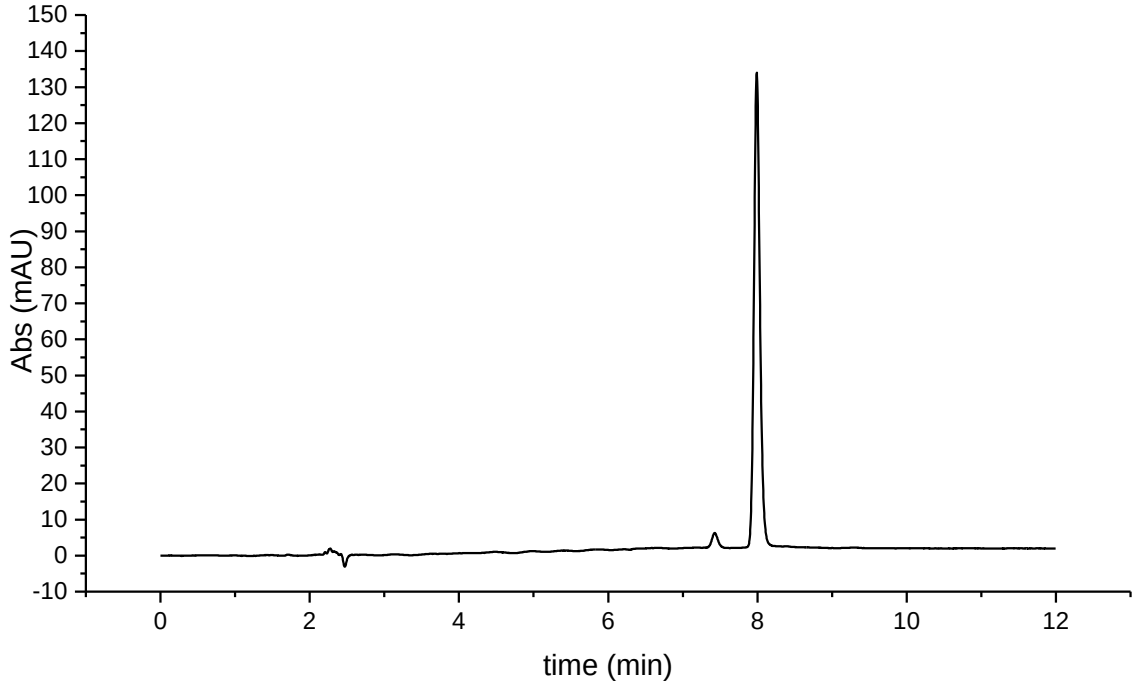
Anexo 12. Mass spectrum (MS/MS), precursor ion *m/z* 275.09 $[M + H]^+$ of reference sample of ketone **2**



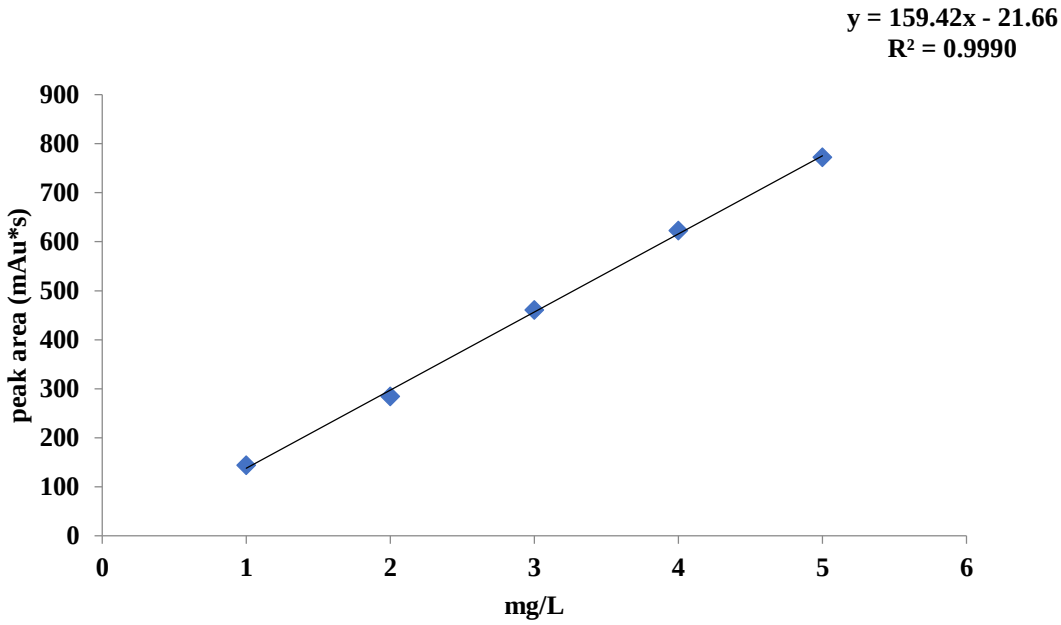
Anexo 13. Chromatogram of reference sample of ketone **1** (344 nm)



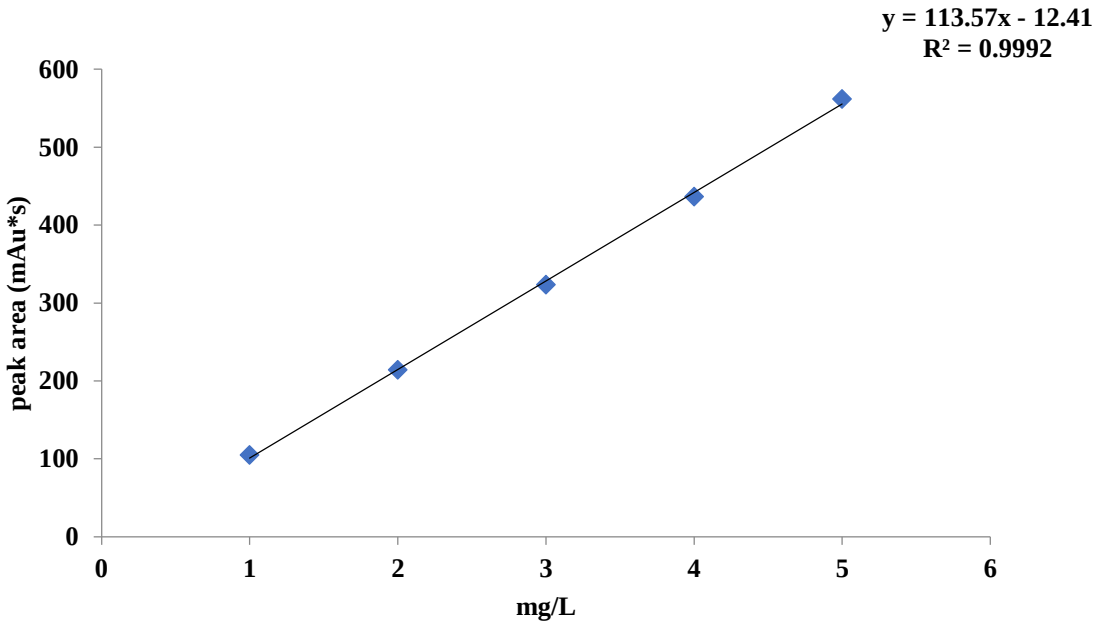
Anexo 14. Chromatogram of reference sample of ketone **2** (328 nm)



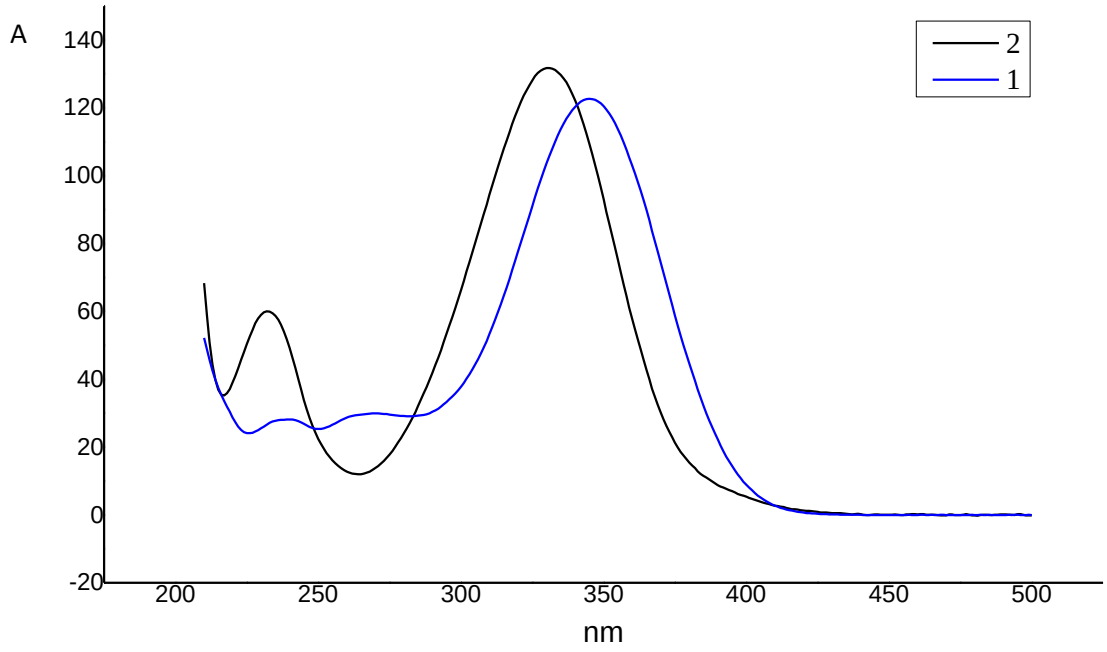
Anexo 15. Analytical curve of reference sample of ketone **1**



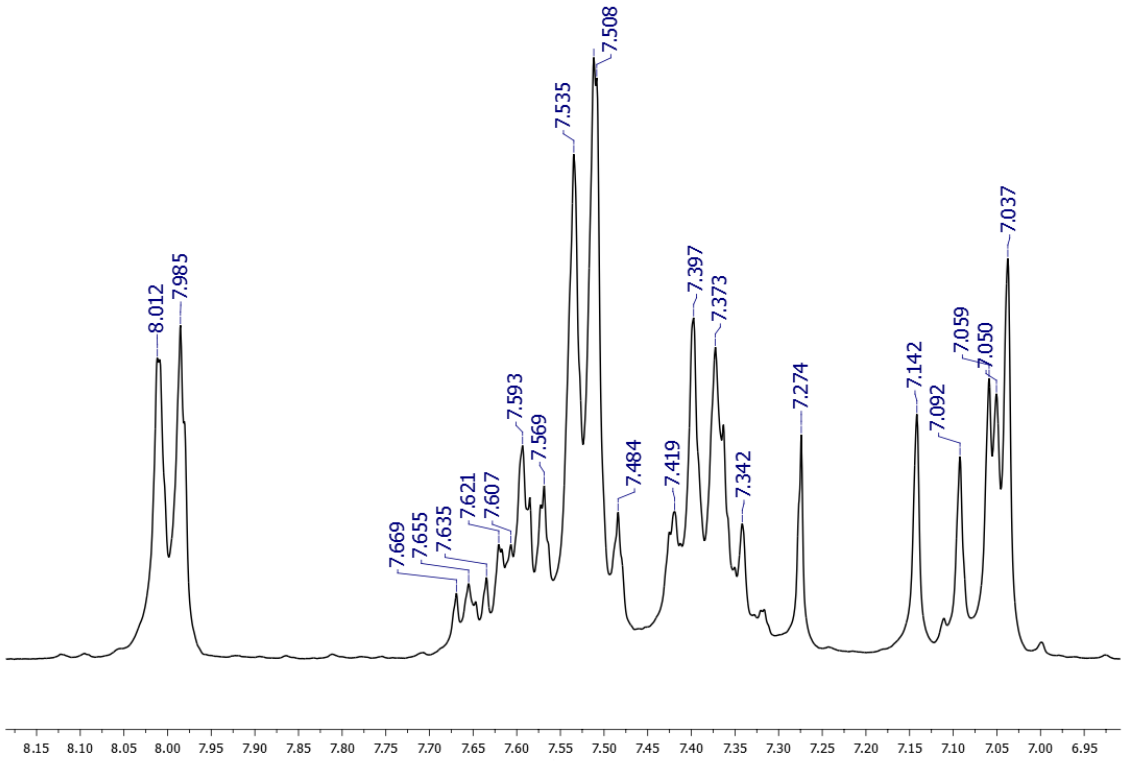
Anexo 16. Analytical curve of reference sample of ketone **2**



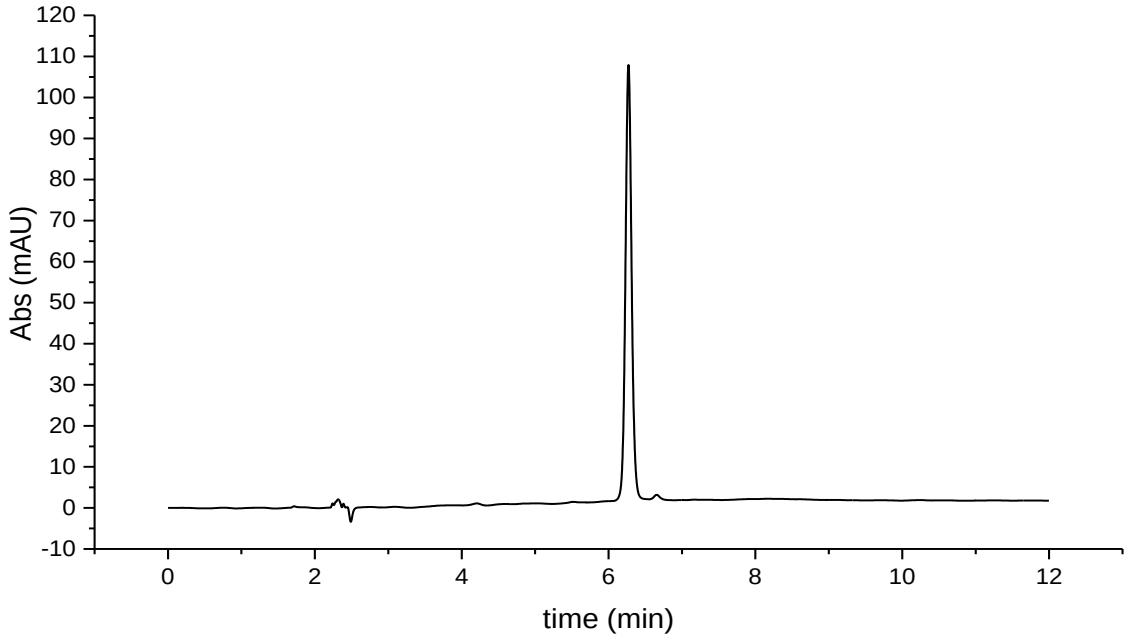
Anexo 17. UV-Vis spectra of reference samples of ketones **1** e **2** from HPLC-PAD experiment



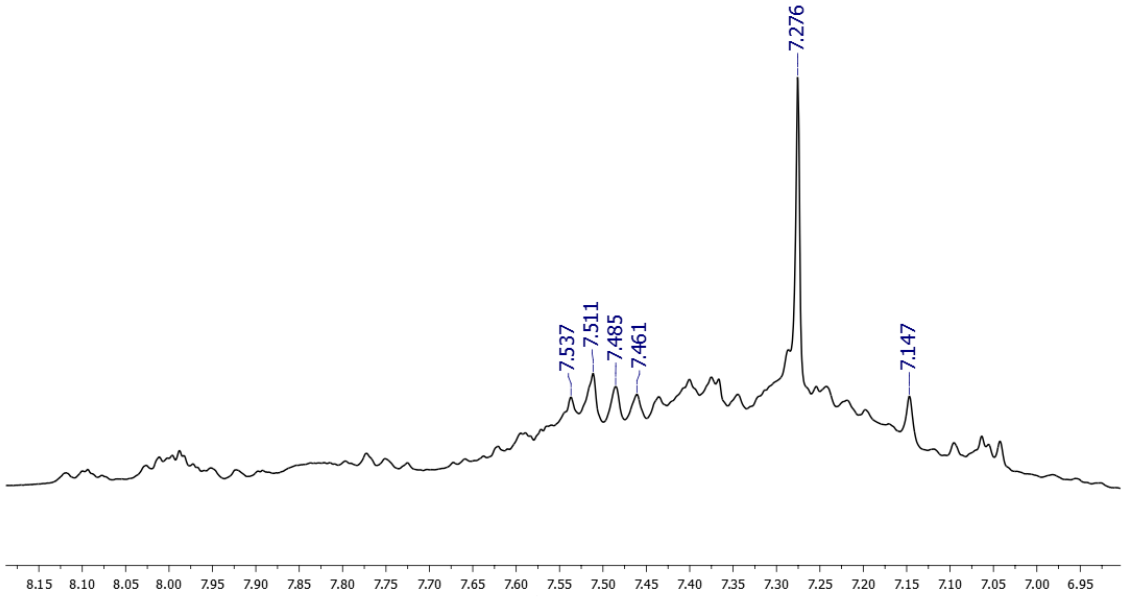
Anexo 18. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in glycerol ($CDCl_3$; 300 MHz)



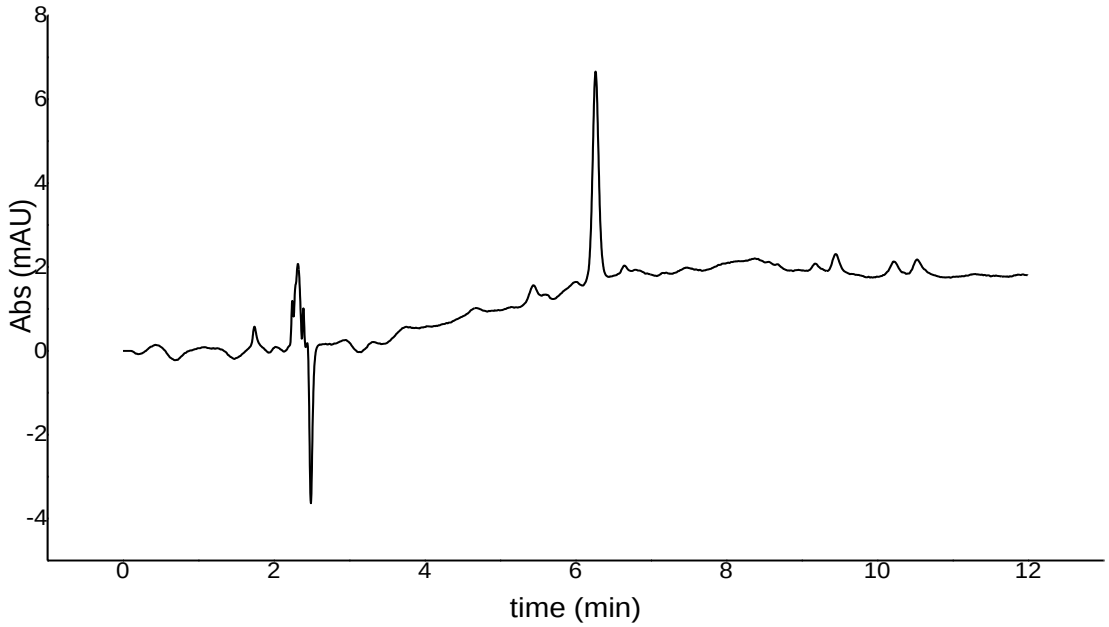
Anexo 19. Chromatogram of ketone **1** synthesized in glycerol (344 nm)



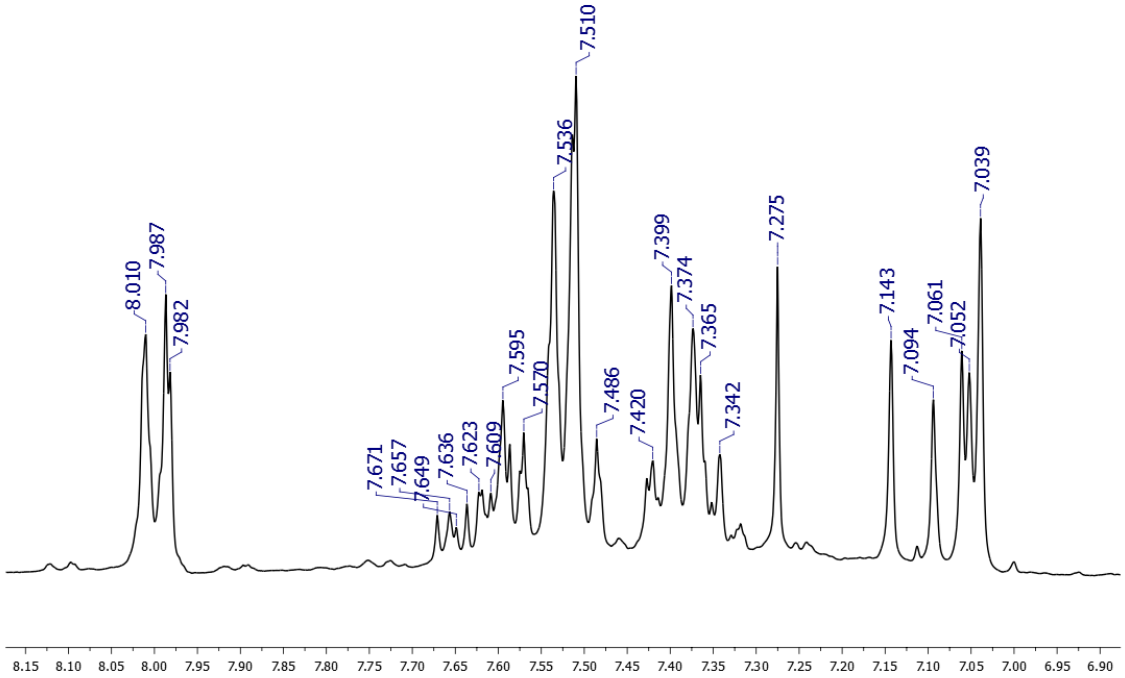
Anexo 20. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in ethanol ($CDCl_3$; 300 MHz)



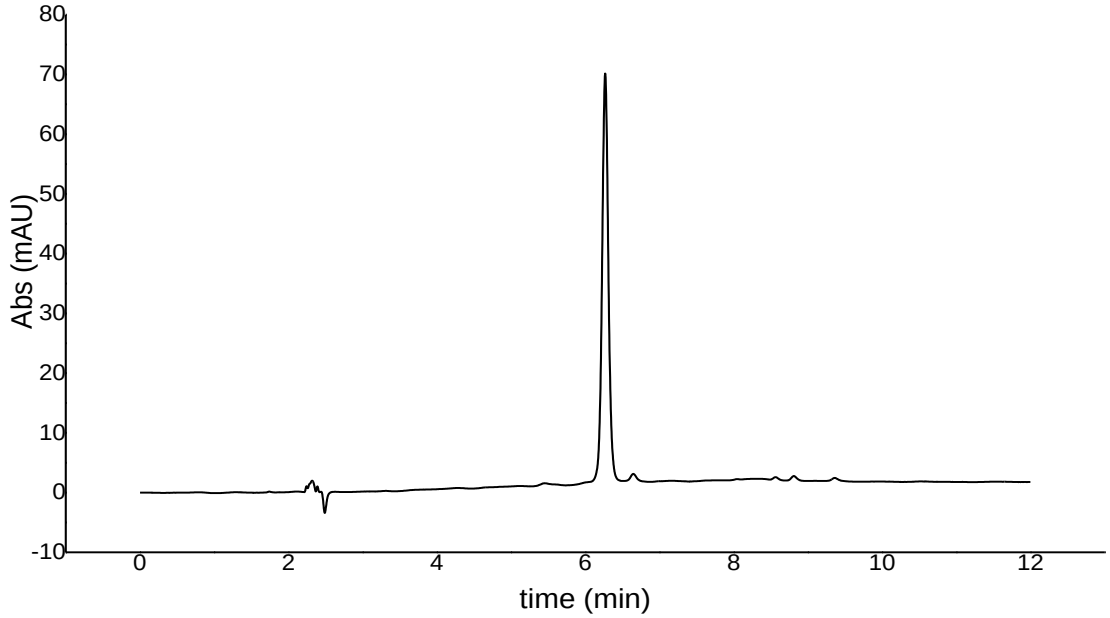
Anexo 21. Chromatogram of ketone **1** synthesized in ethanol (344 nm)



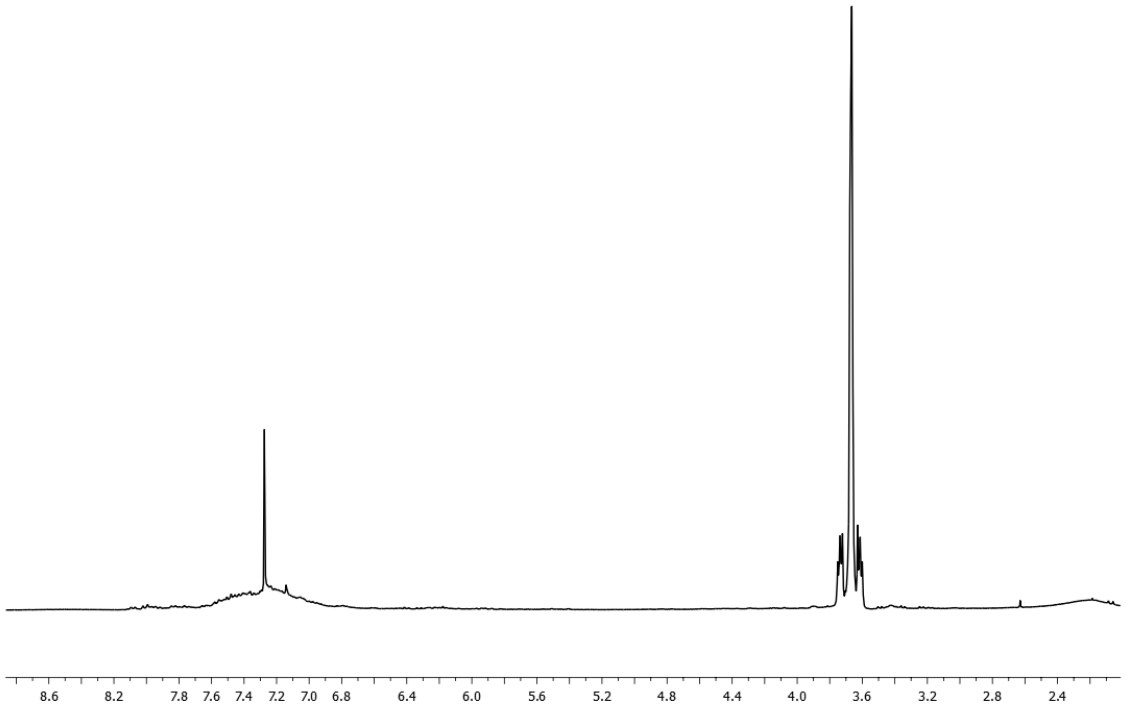
Anexo 22. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in methanol ($CDCl_3$; 300 MHz)



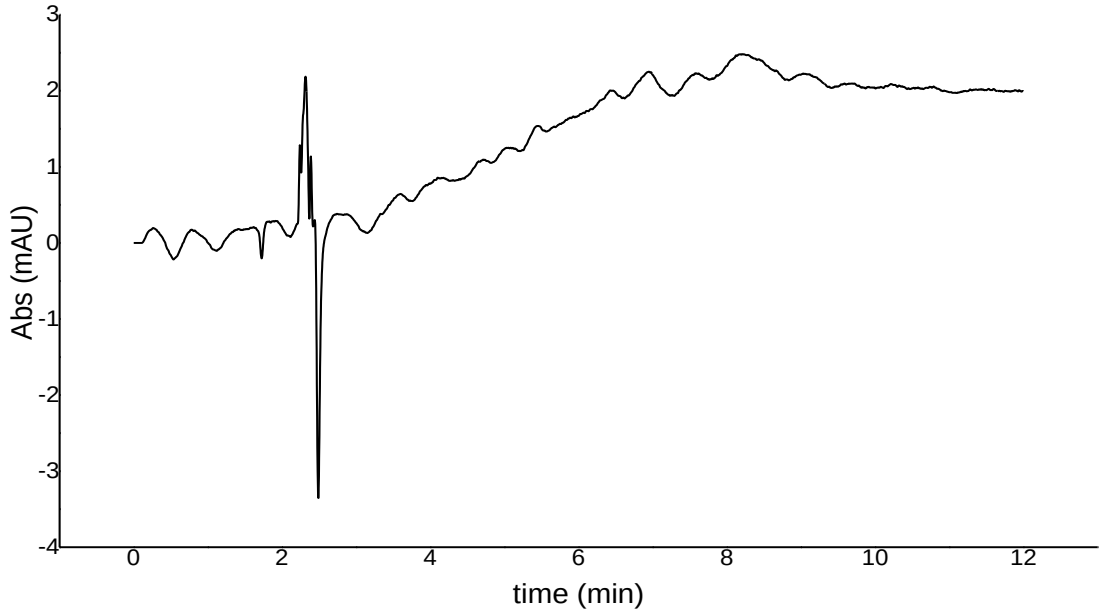
Anexo 23. Chromatogram of ketone **1** synthesized in methanol (344 nm)



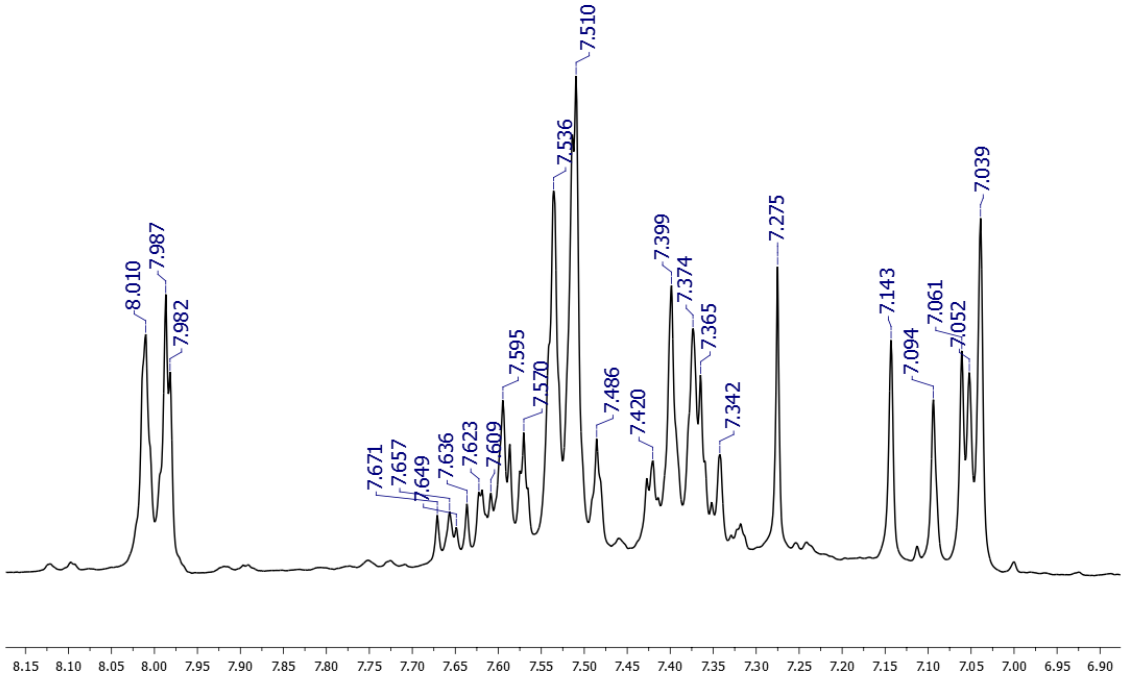
Anexo 24. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in PEG-400 ($CDCl_3$; 300 MHz)



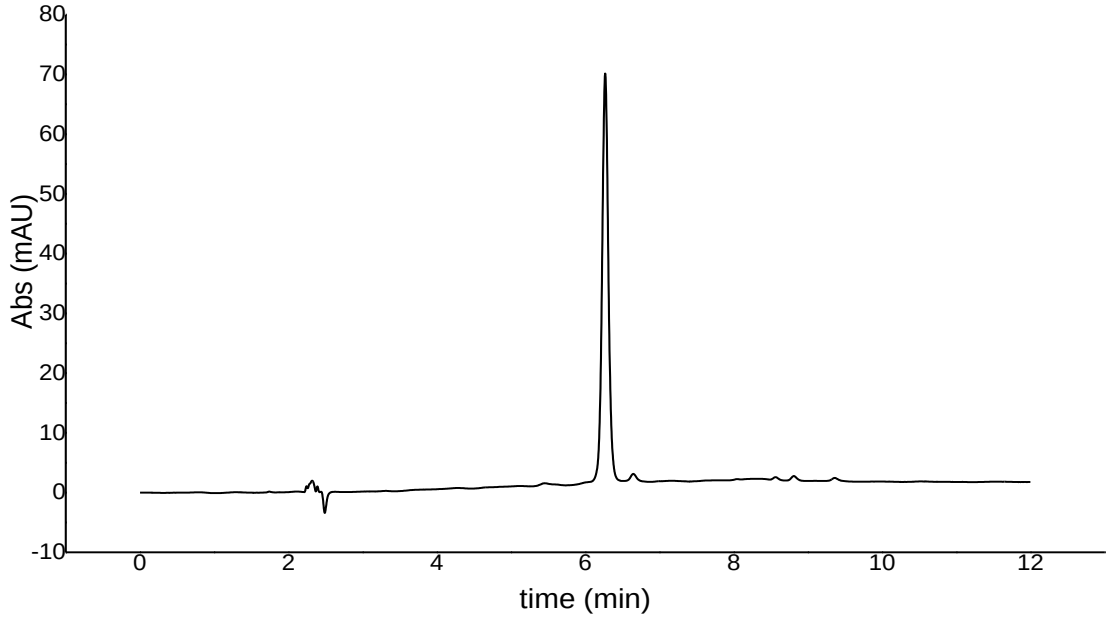
Anexo 25. Chromatogram of ketone **1** synthesized in PEG-400 (344 nm)



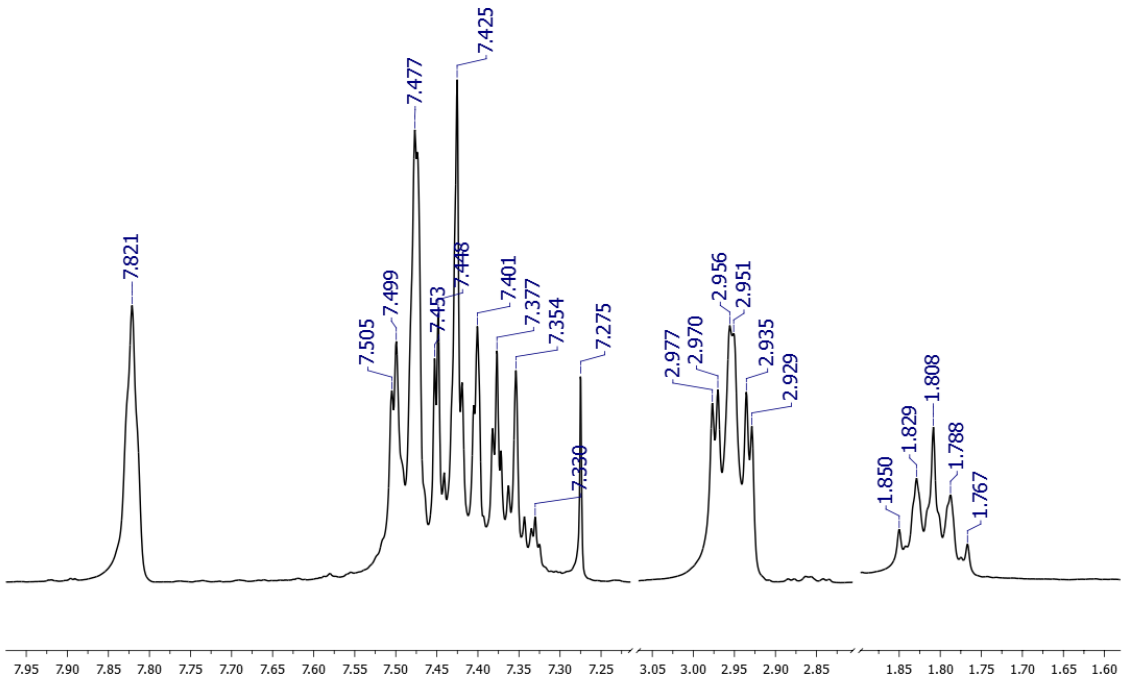
Anexo 26. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in water ($CDCl_3$; 300 MHz)



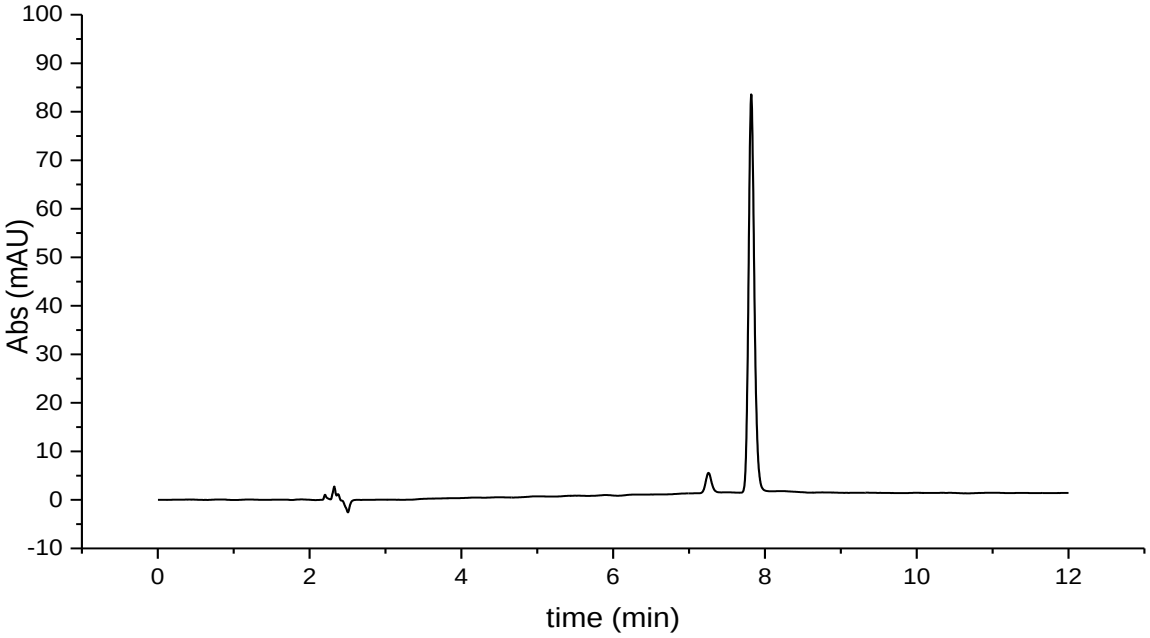
Anexo 27. Chromatogram of ketone **1** synthesized in water (344 nm)



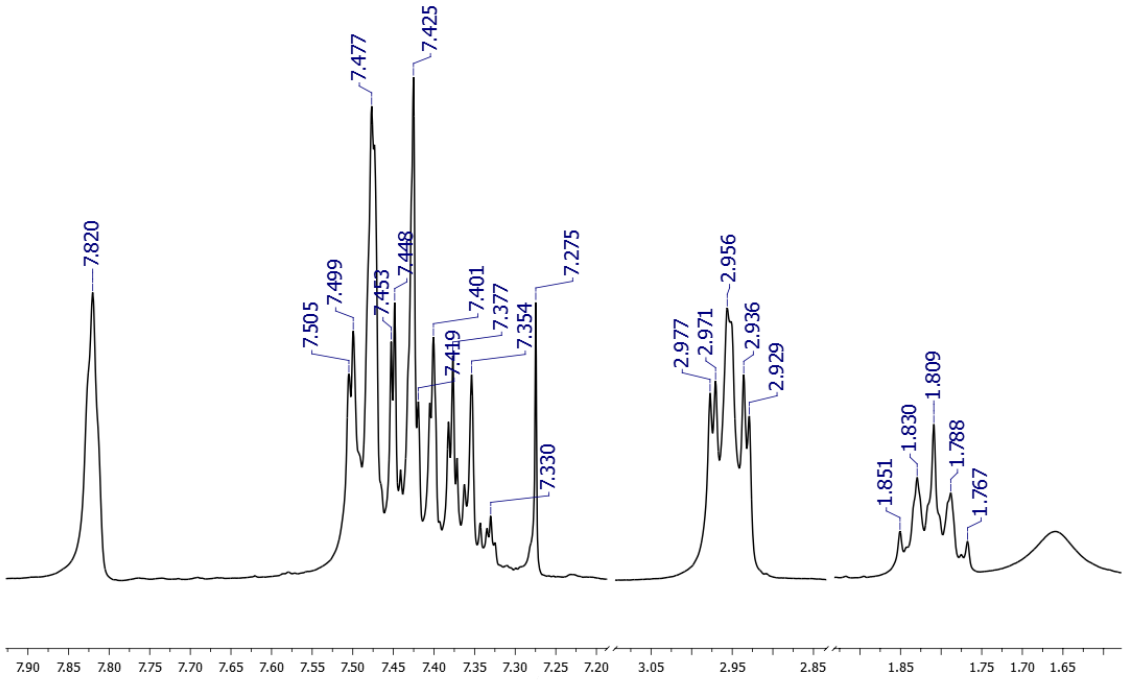
Anexo 28. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in glycerol ($CDCl_3$; 300 MHz)



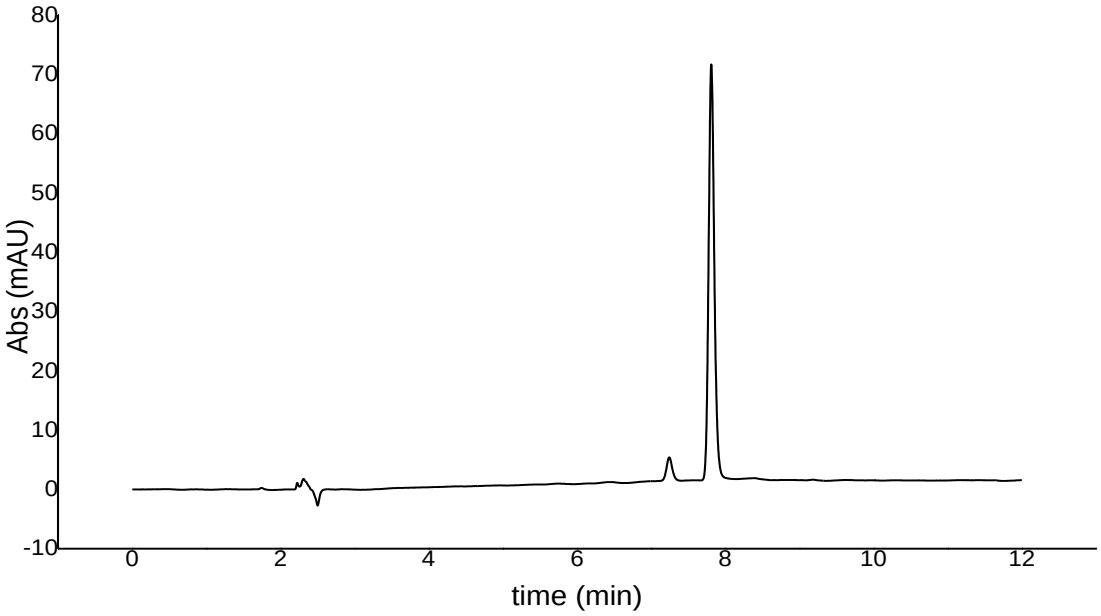
Anexo 29. Chromatogram of ketone **2** synthesized in glycerol (328 nm)



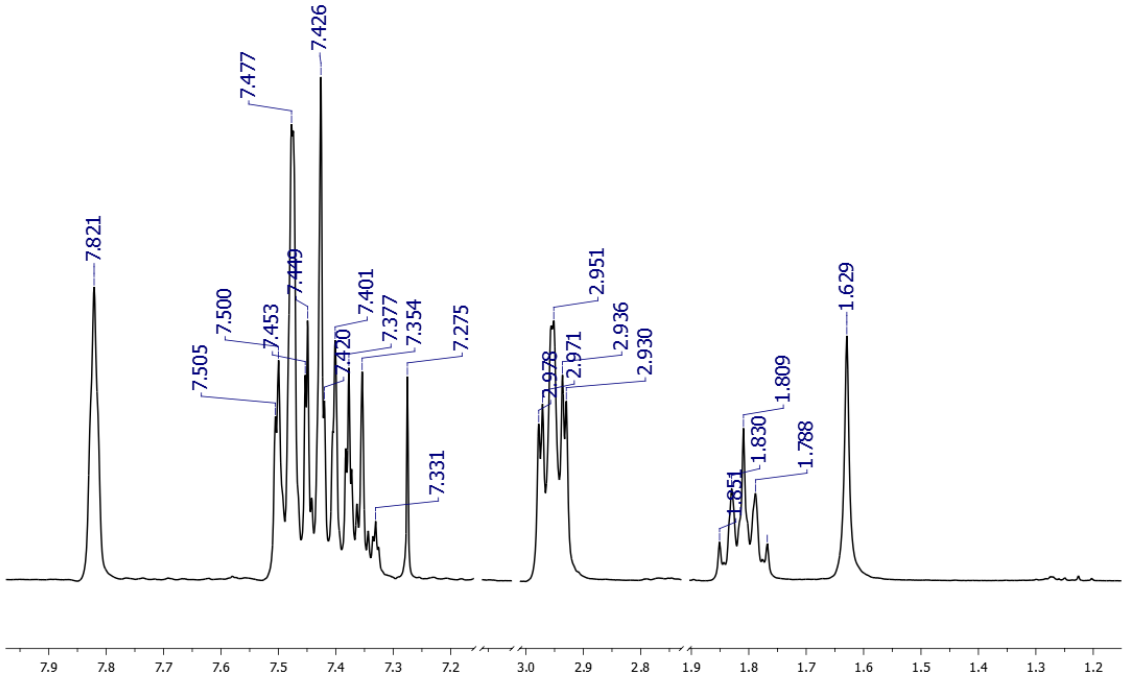
Anexo 30. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in ethanol ($CDCl_3$; 300 MHz)



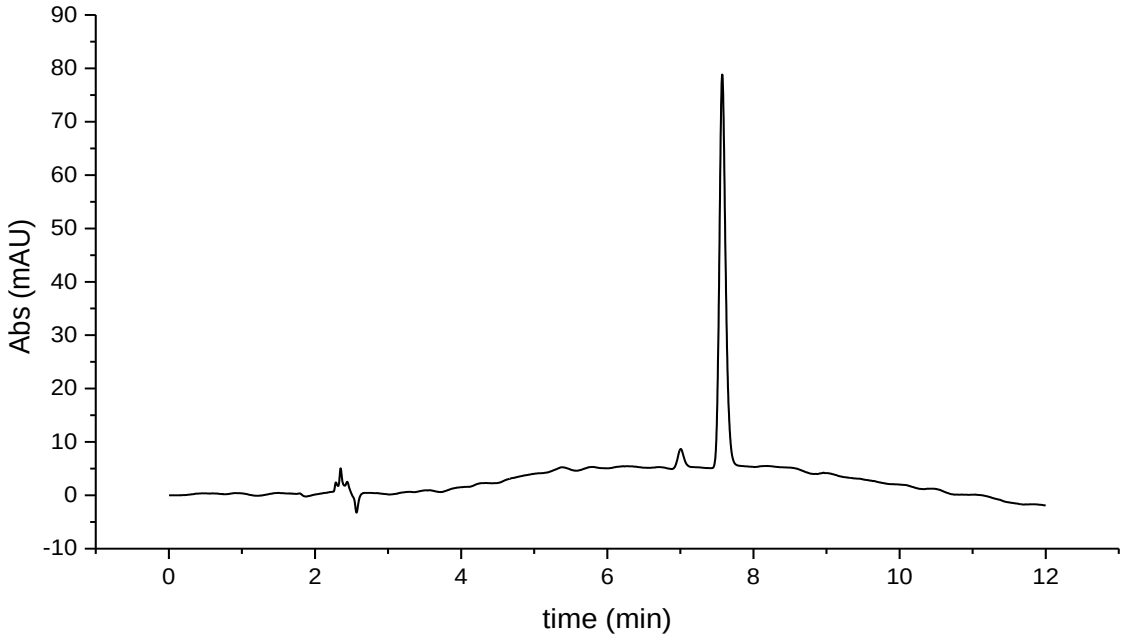
Anexo 31. Chromatogram of ketone **2** synthesized in ethanol (328 nm)



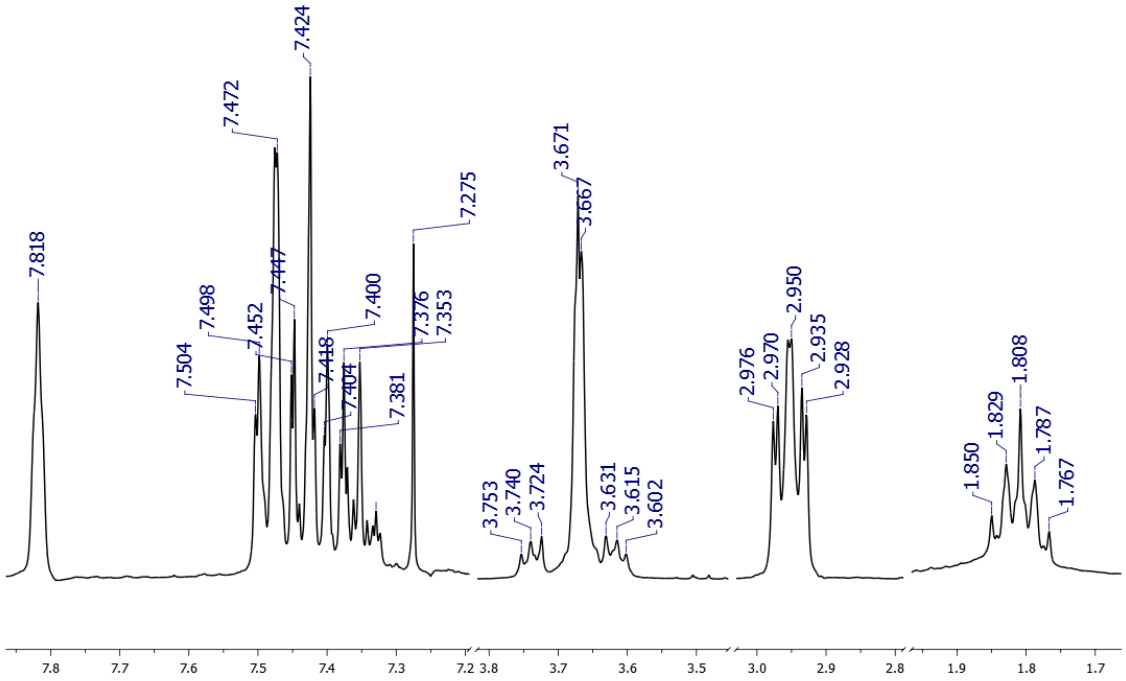
Anexo 32. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in methanol ($CDCl_3$; 300 MHz)



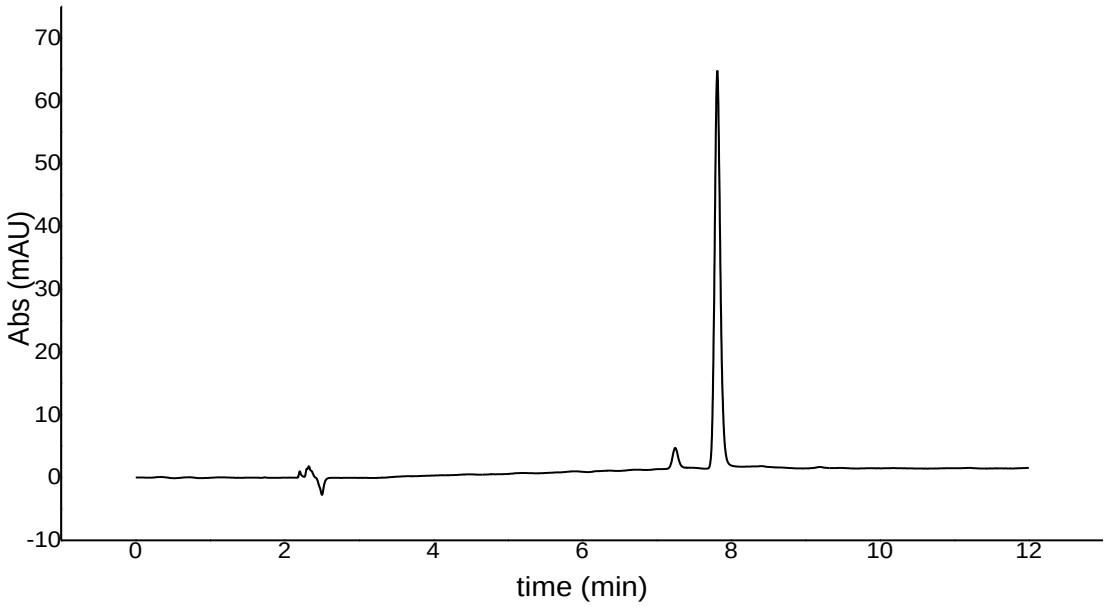
Anexo 33. Chromatogram of ketone **2** synthesized in methanol (328 nm)



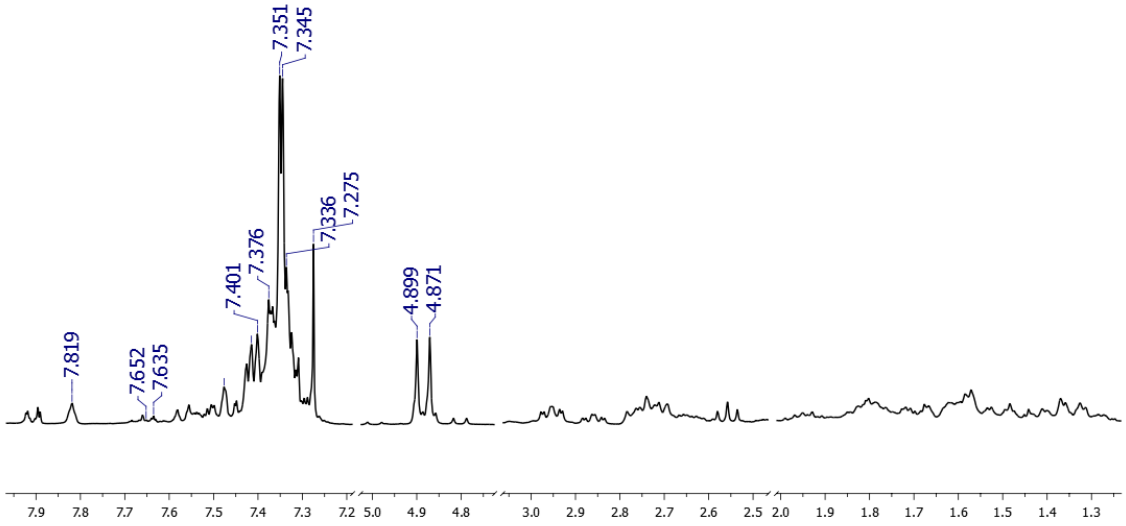
Anexo 34. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in PEG-400 ($CDCl_3$; 300 MHz)



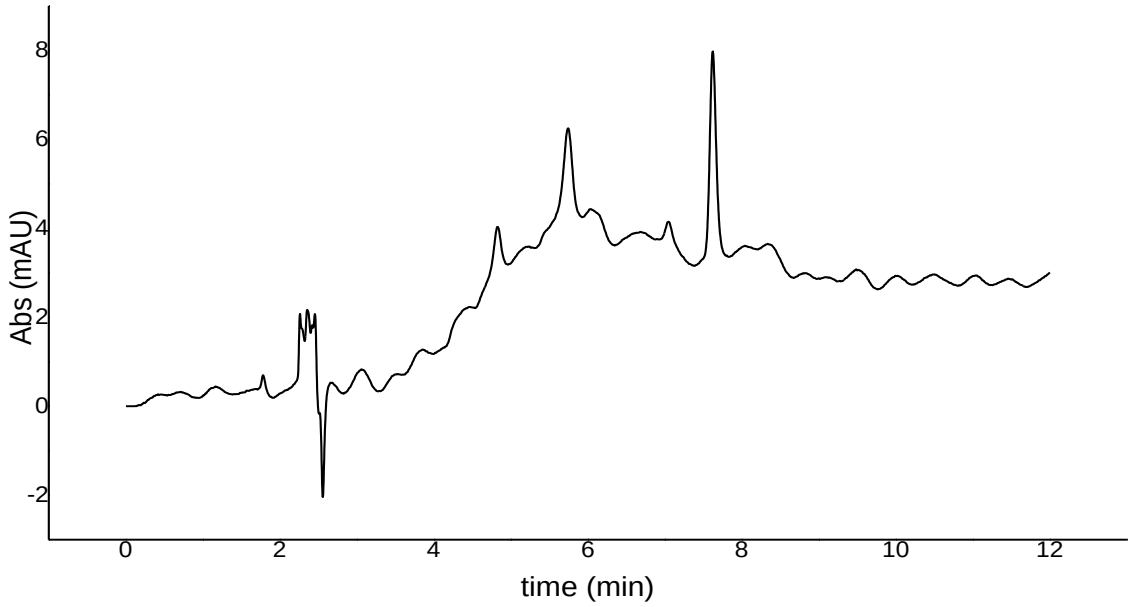
Anexo 35. Chromatogram of ketone **2** synthesized in PEG-400 (328 nm)



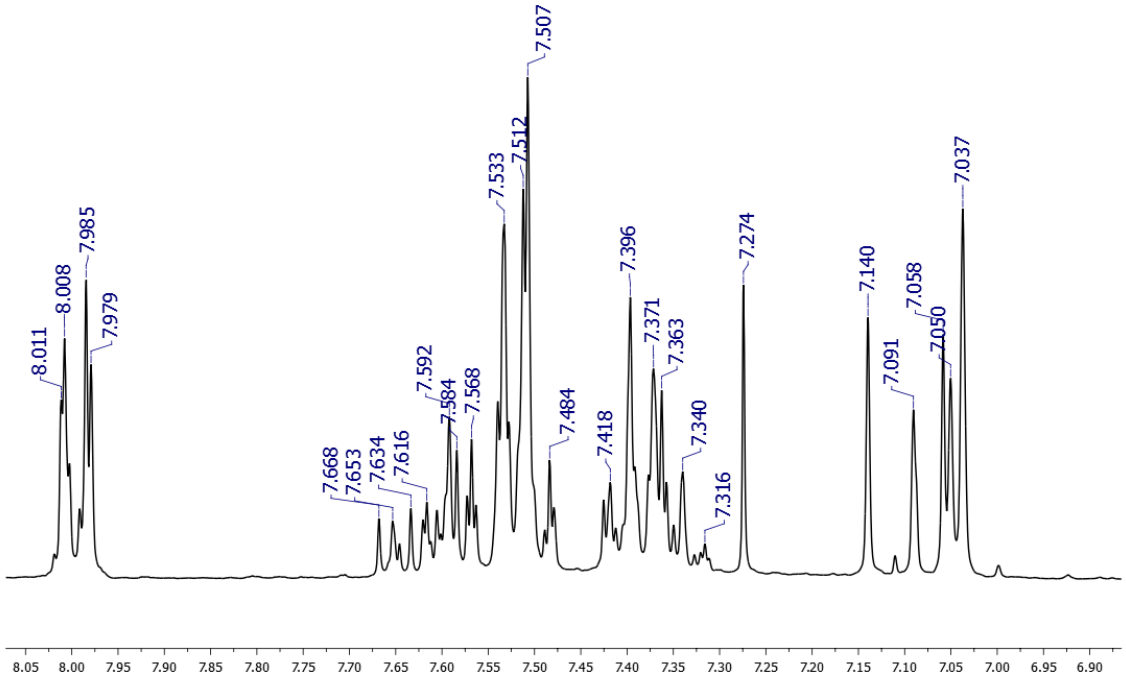
Anexo 36. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in water ($CDCl_3$; 300 MHz)



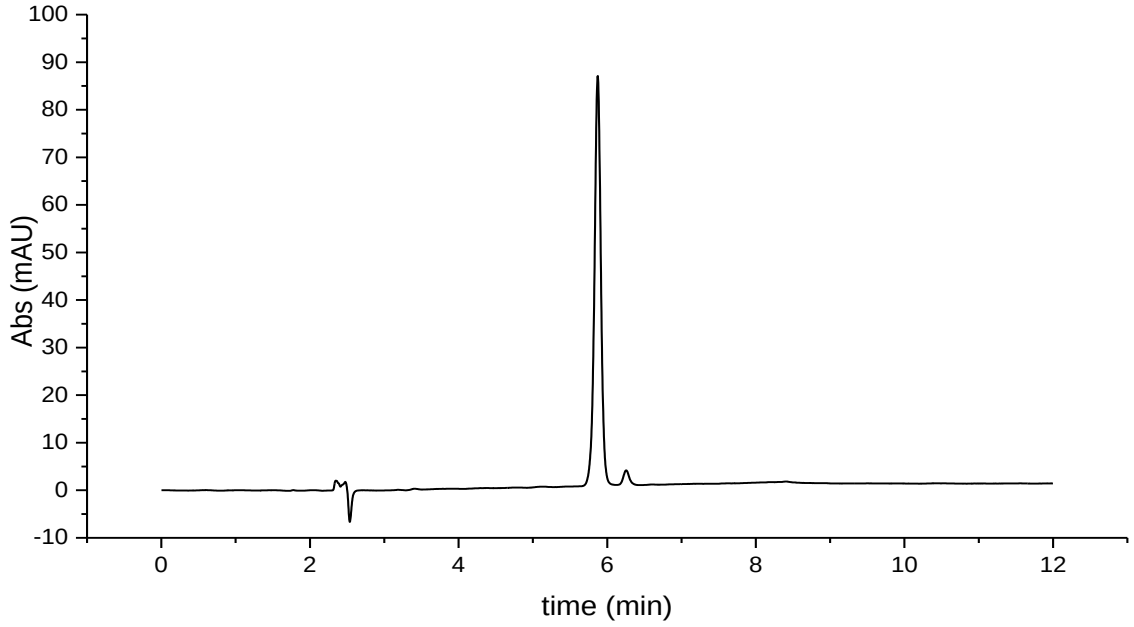
Anexo 37. Chromatogram of ketone **2** synthesized in water (328 nm)



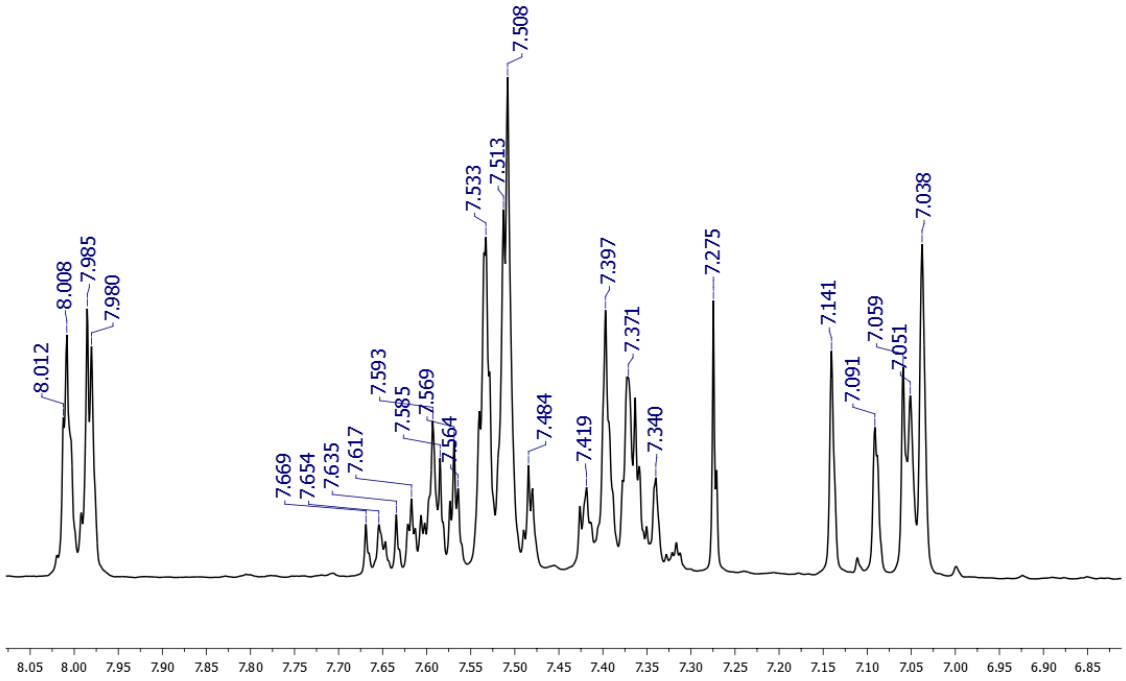
Anexo 38. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in crude glycerol from castor oil ($CDCl_3$; 300 MHz)



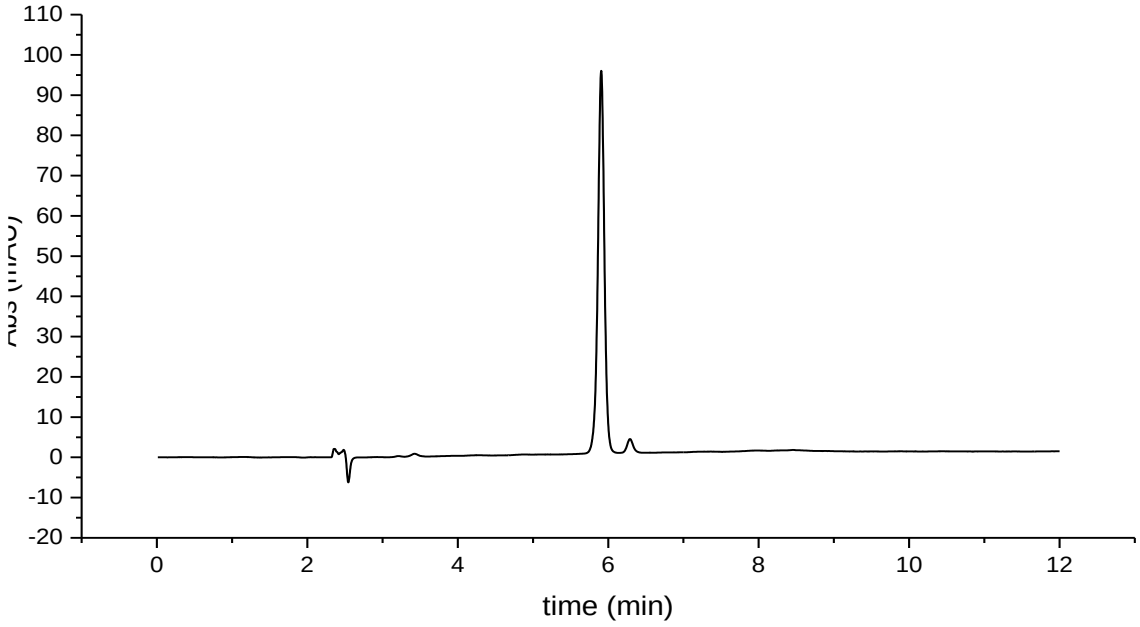
Anexo 39. Chromatogram of ketone **1** synthesized in crude glycerol from castor oil (344 nm)



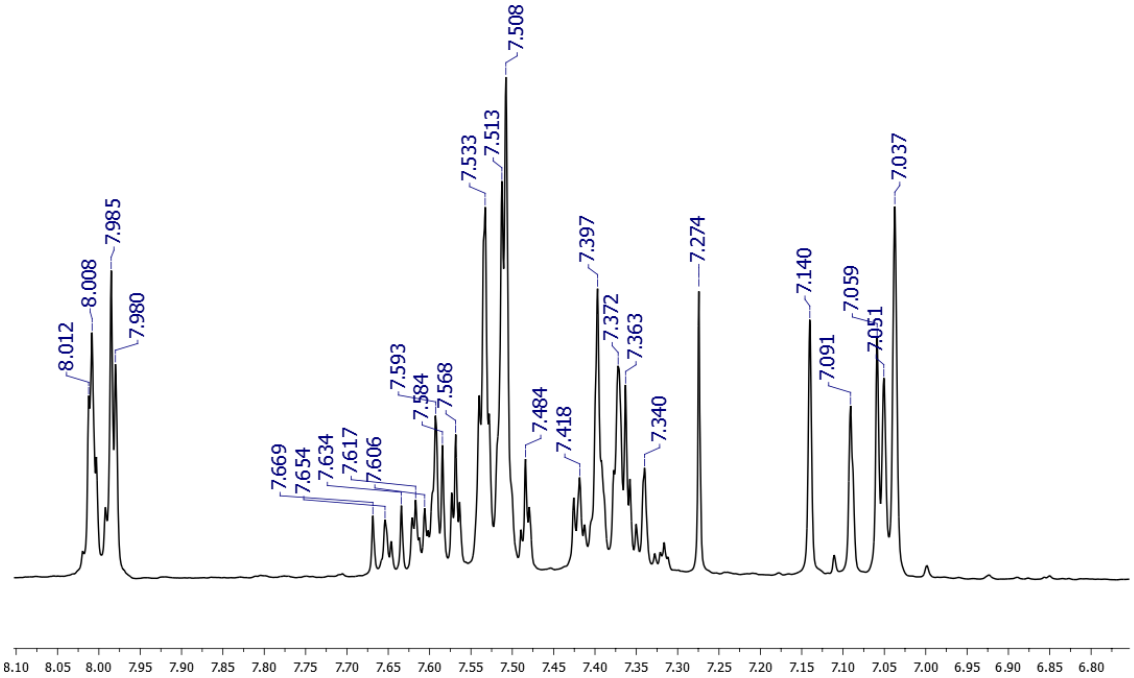
Anexo 40. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in crude glycerol from corn oil ($CDCl_3$; 300 MHz)



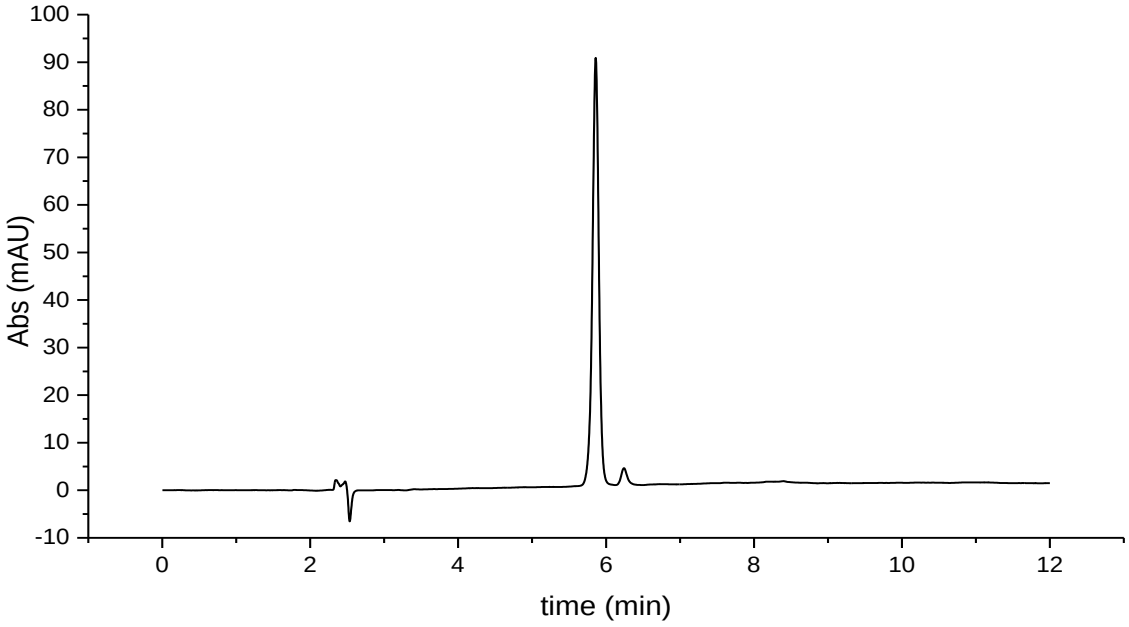
Anexo 41. Chromatogram of ketone **1** synthesized in crude glycerol from corn oil (344 nm)



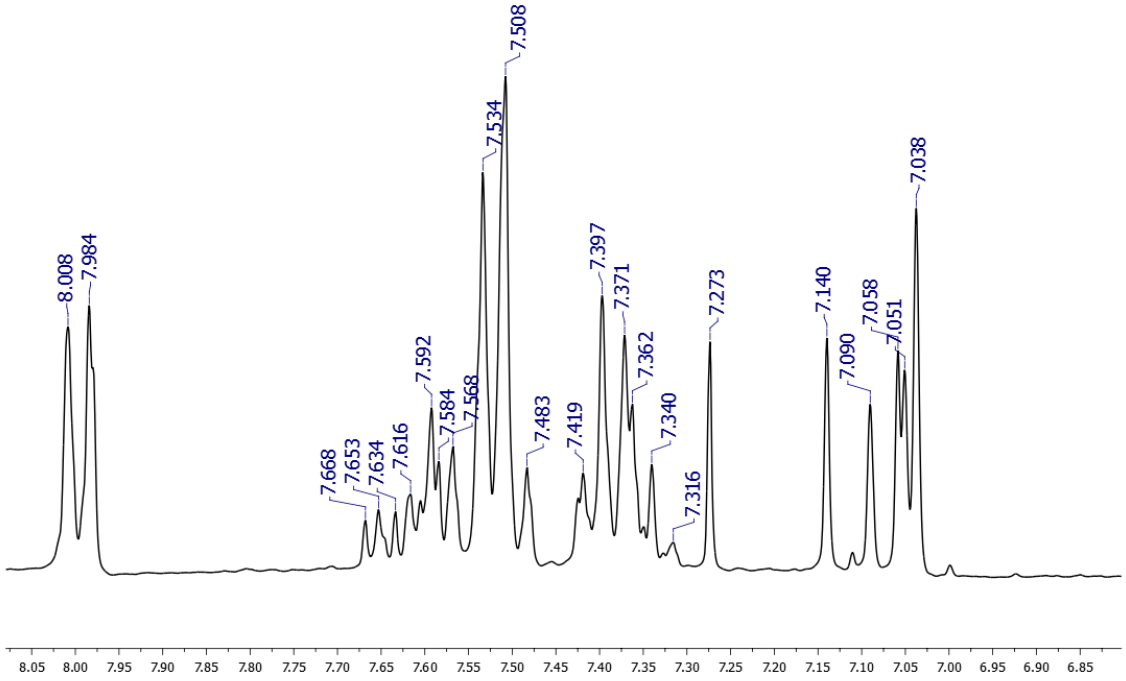
Anexo 42. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in crude glycerol from soybean oil ($CDCl_3$; 300 MHz)



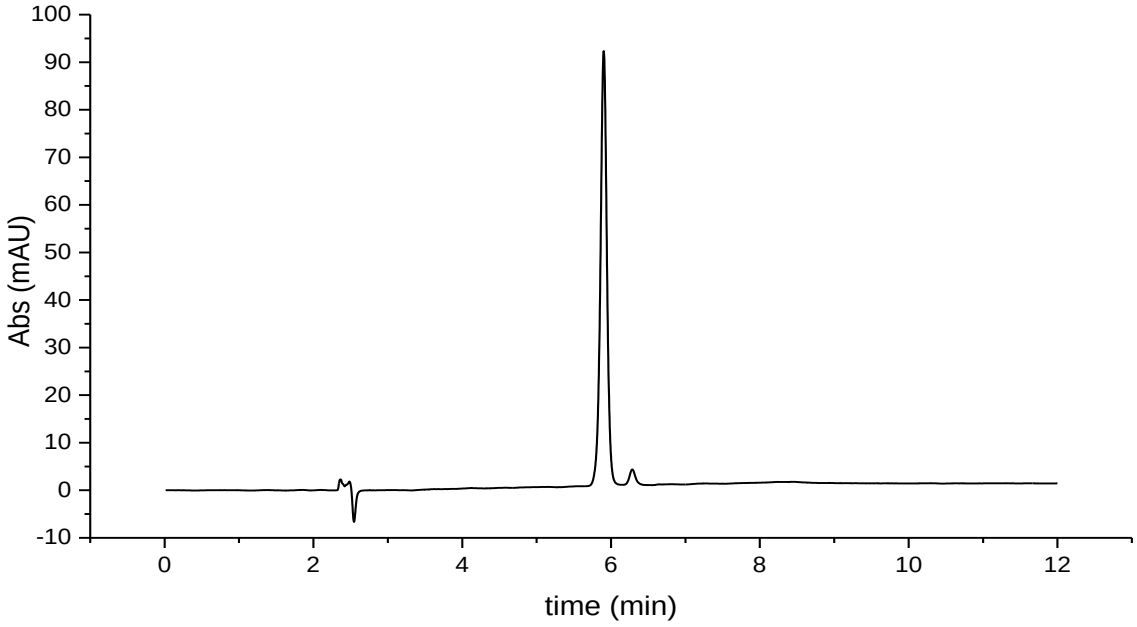
Anexo 43. Chromatogram of ketone **1** synthesized in crude glycerol from soybean oil (344 nm)



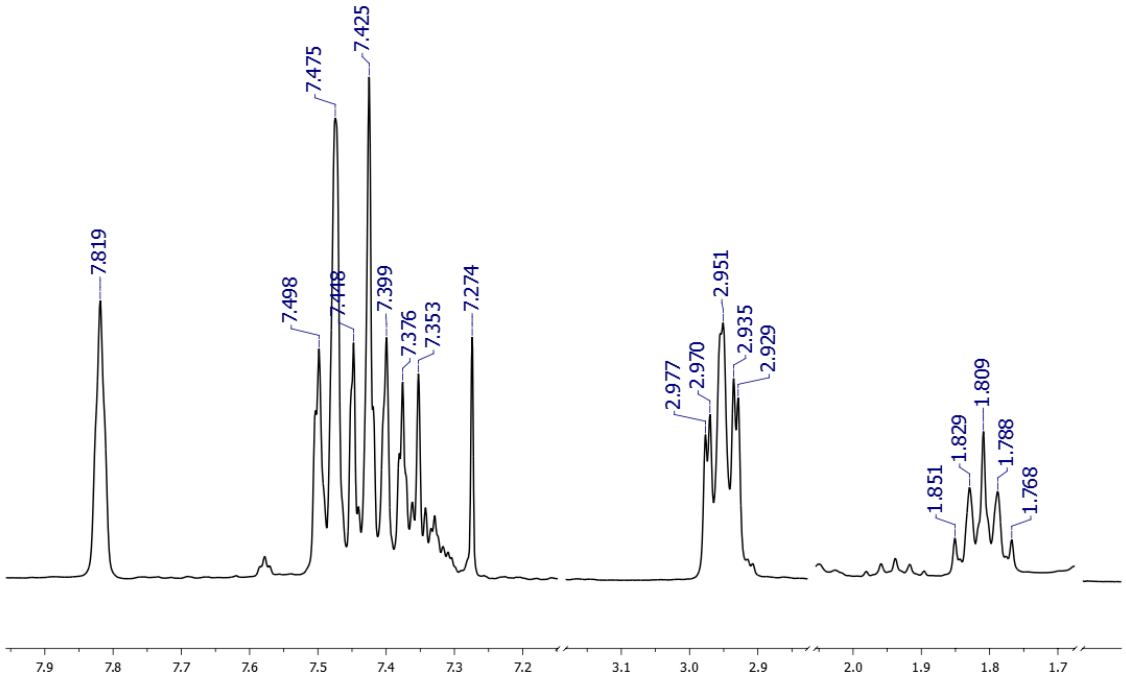
Anexo 44. Expansion of ^{1}H NMR spectrum of ketone **1** synthesized in crude glycerol from sunflower oil ($CDCl_3$; 300 MHz)



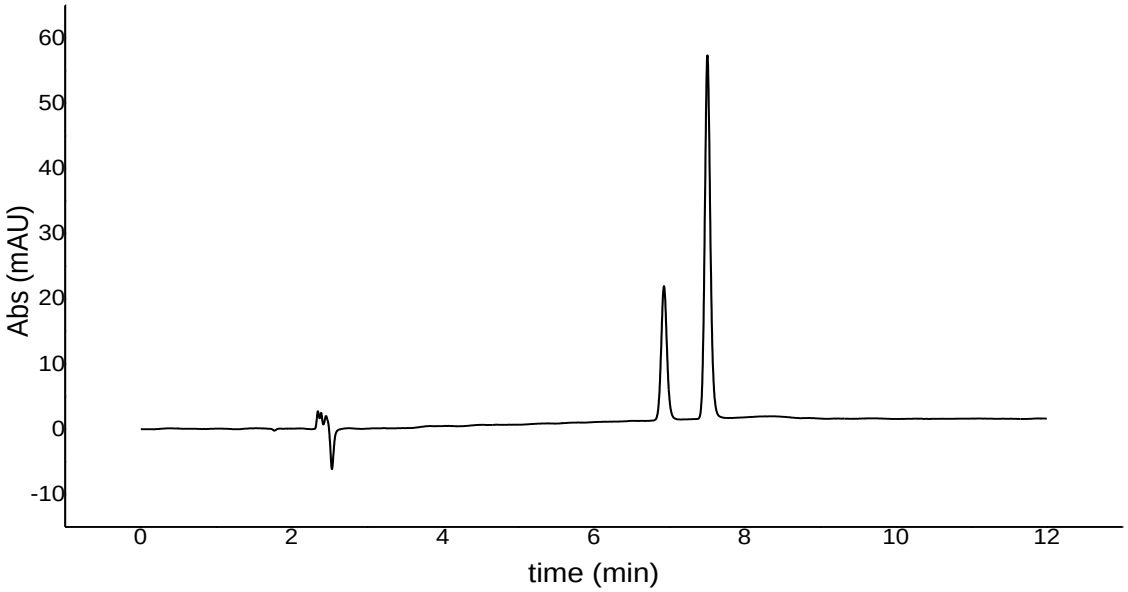
Anexo 45. Chromatogram of ketone **1** synthesized in crude glycerol from sunflower oil (344 nm)



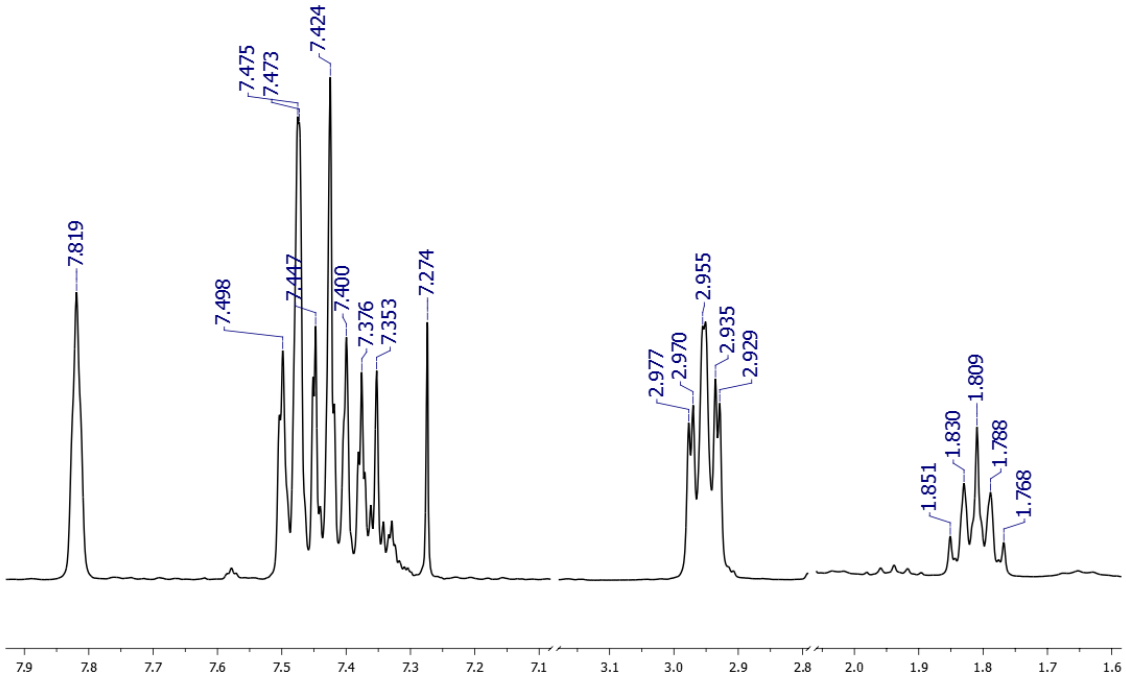
Anexo 46. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in crude glycerol from castor oil ($CDCl_3$; 300 MHz)



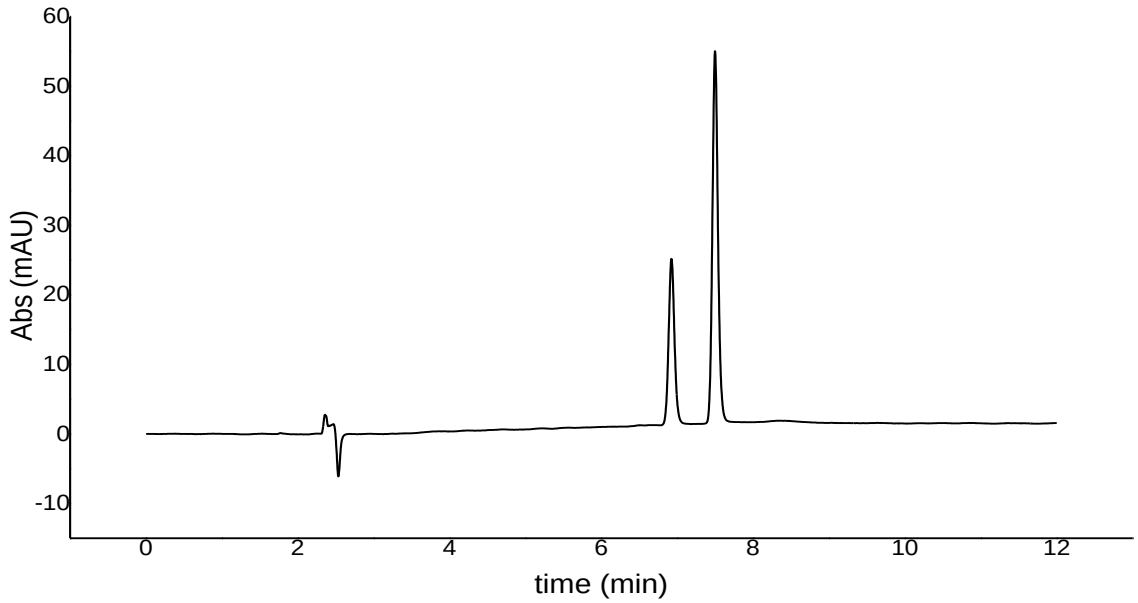
Anexo 47. Chromatogram of ketone **2** synthesized in crude glycerol from castor oil (328 nm)



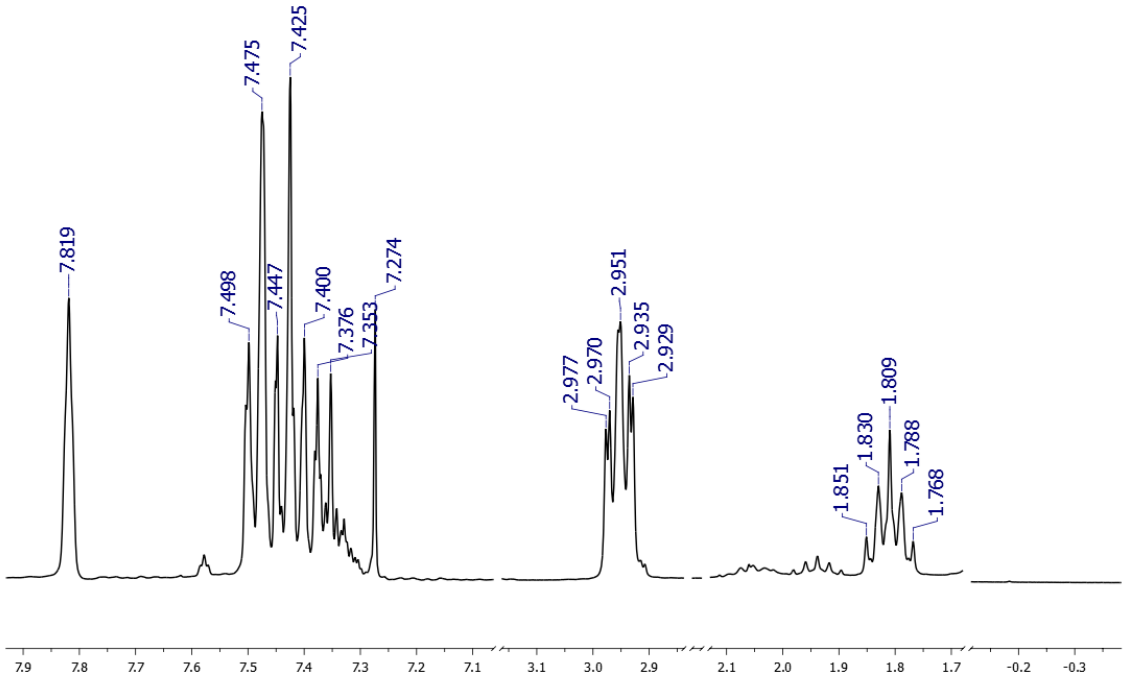
Anexo 48. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in crude glycerol from corn oil ($CDCl_3$; 300 MHz)



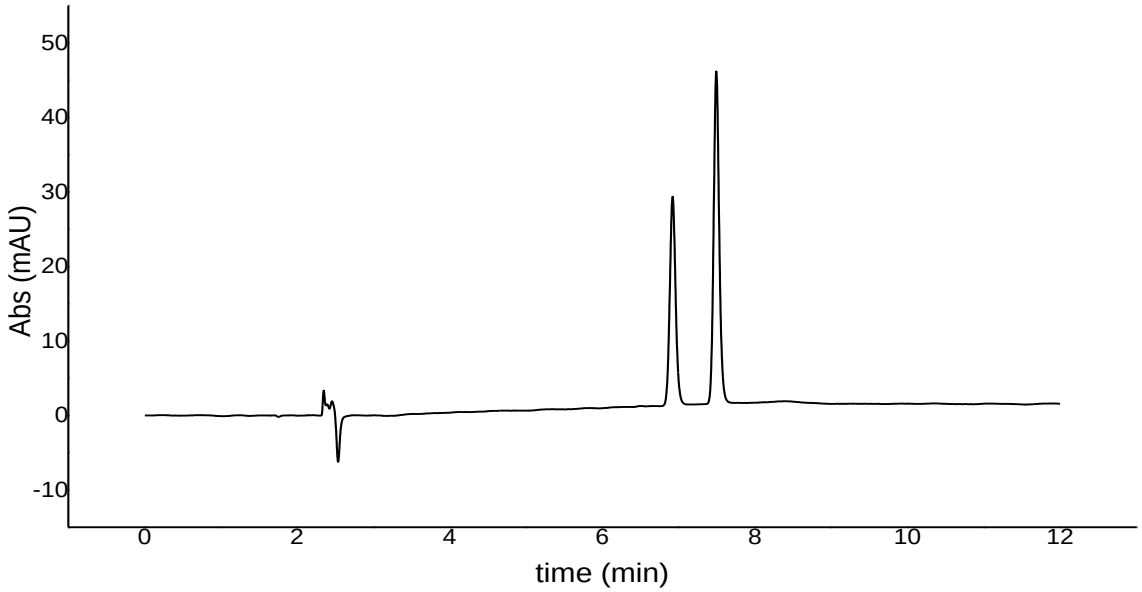
Anexo 49. Chromatogram of ketone **2** synthesized in crude glycerol from corn oil (328 nm)



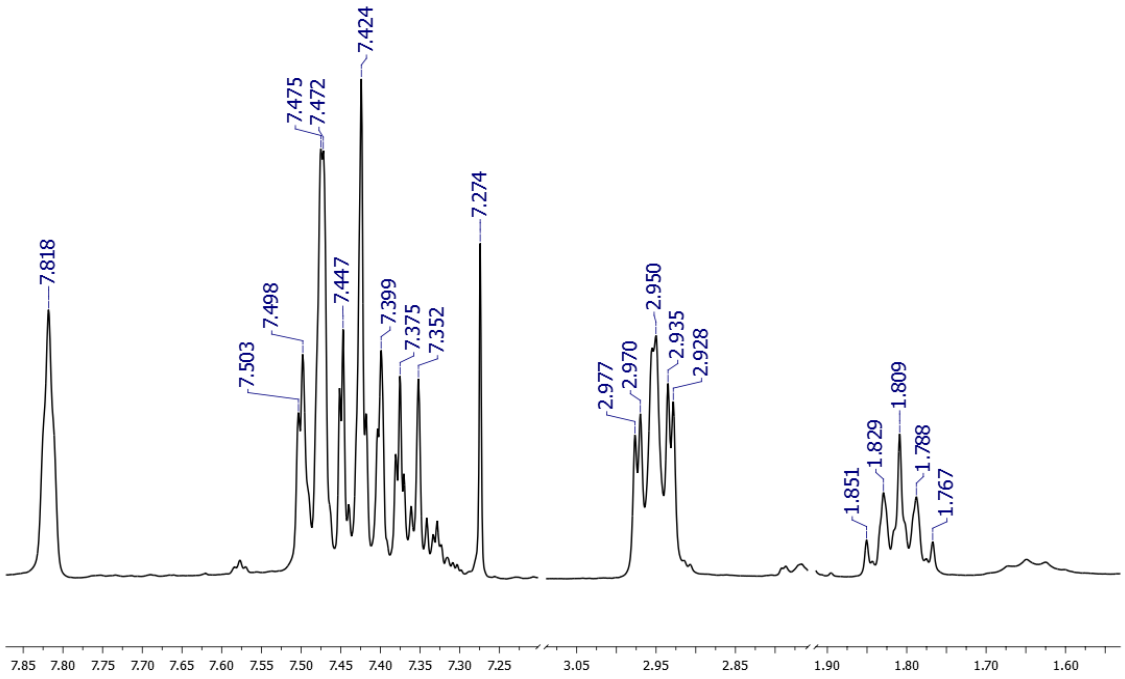
Anexo 50. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in crude glycerol from soybean oil ($CDCl_3$; 300 MHz)



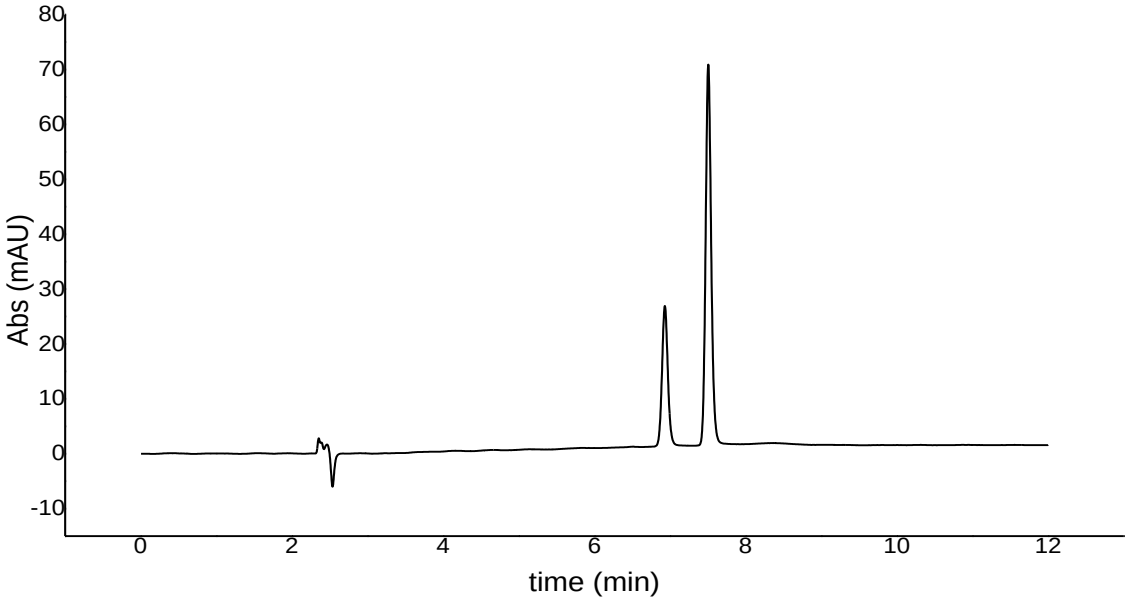
Anexo 51. Chromatogram of ketone **2** synthesized in crude glycerol from soybean oil (328 nm)



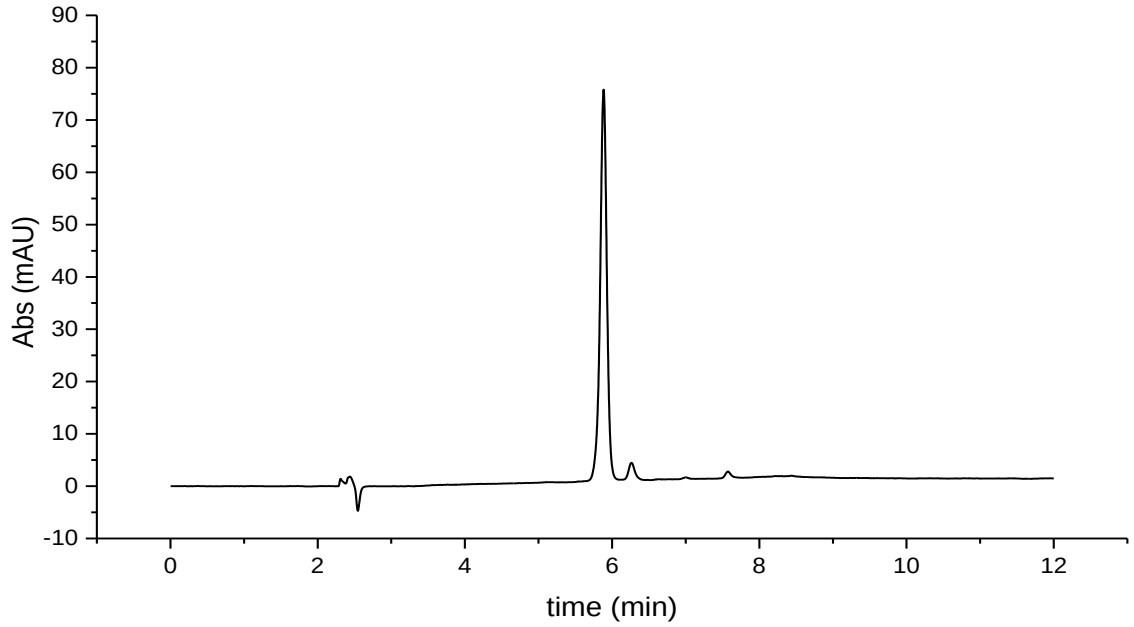
Anexo 52. Expansion of ^{1}H NMR spectrum of ketone **2** synthesized in crude glycerol from sunflower oil ($CDCl_3$; 300 MHz)



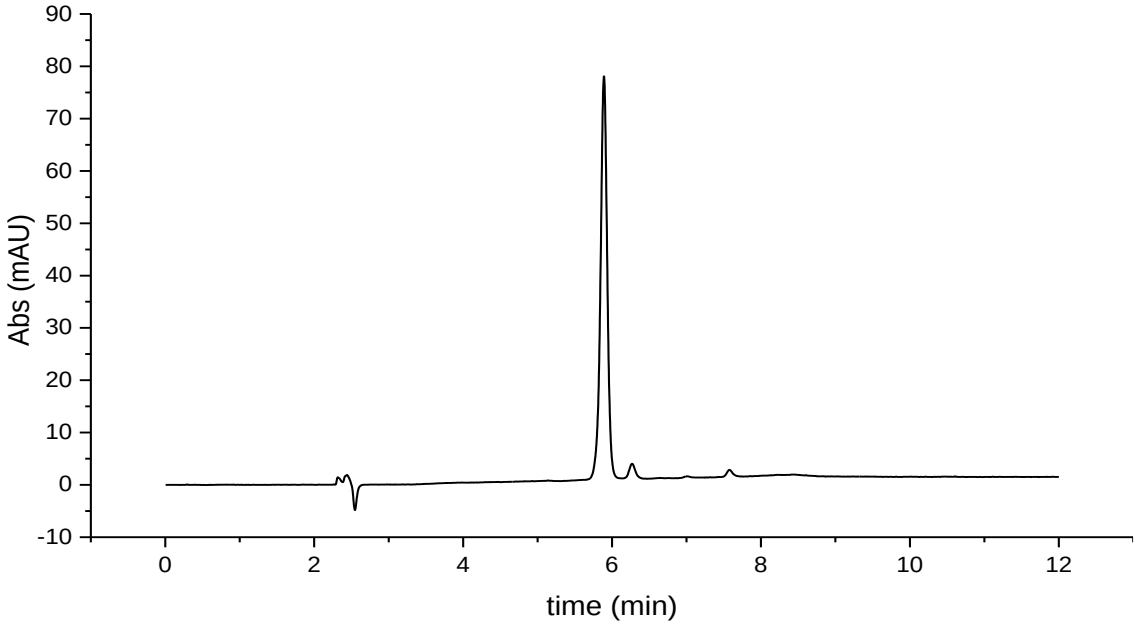
Anexo 53. Chromatogram of ketone **2** synthesized in crude glycerol from sunflower oil (328 nm)



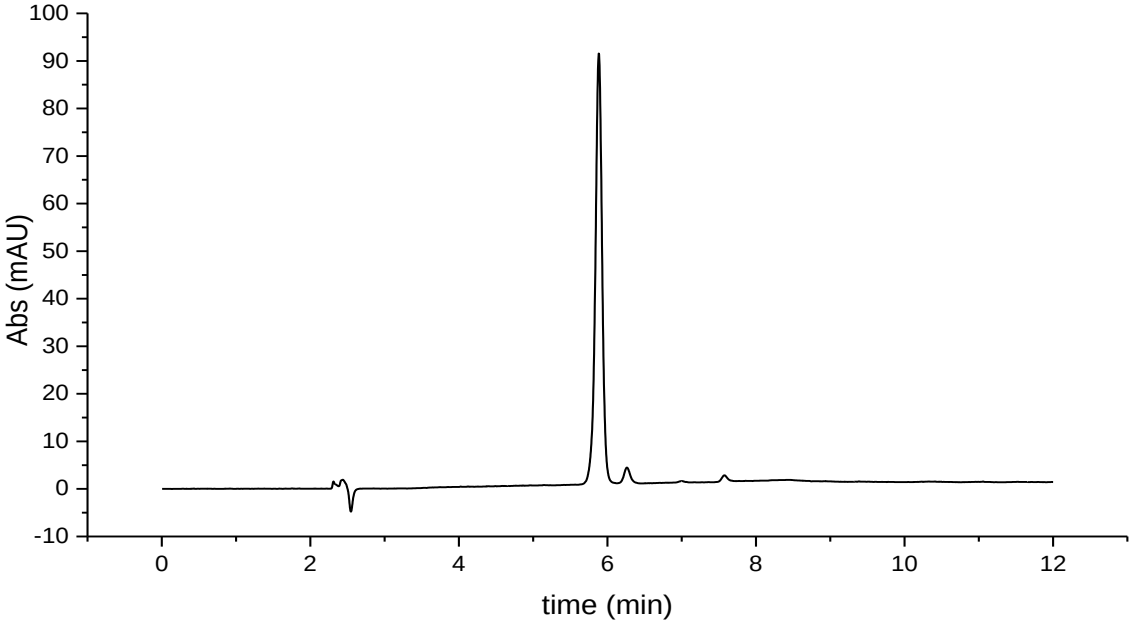
Anexo 54. Chromatogram of ketone **1** synthesized in crude glycerol from corn oil (Cycle 1, 344 nm)



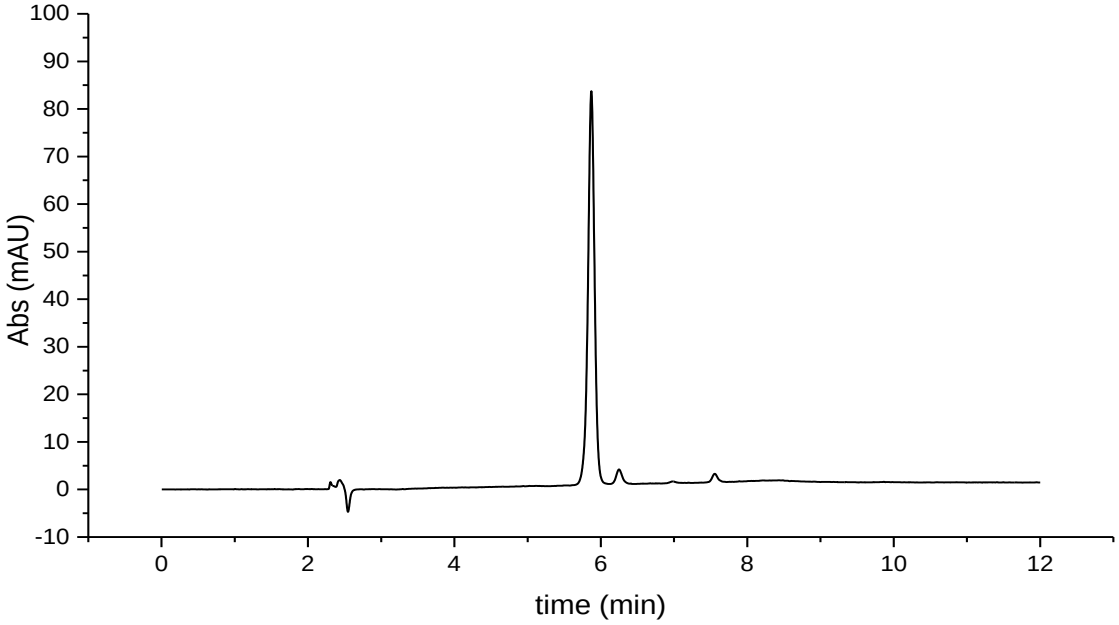
Anexo 55. Chromatogram of ketone **1** synthesized in crude glycerol from corn oil (Cycle 2, 344 nm)



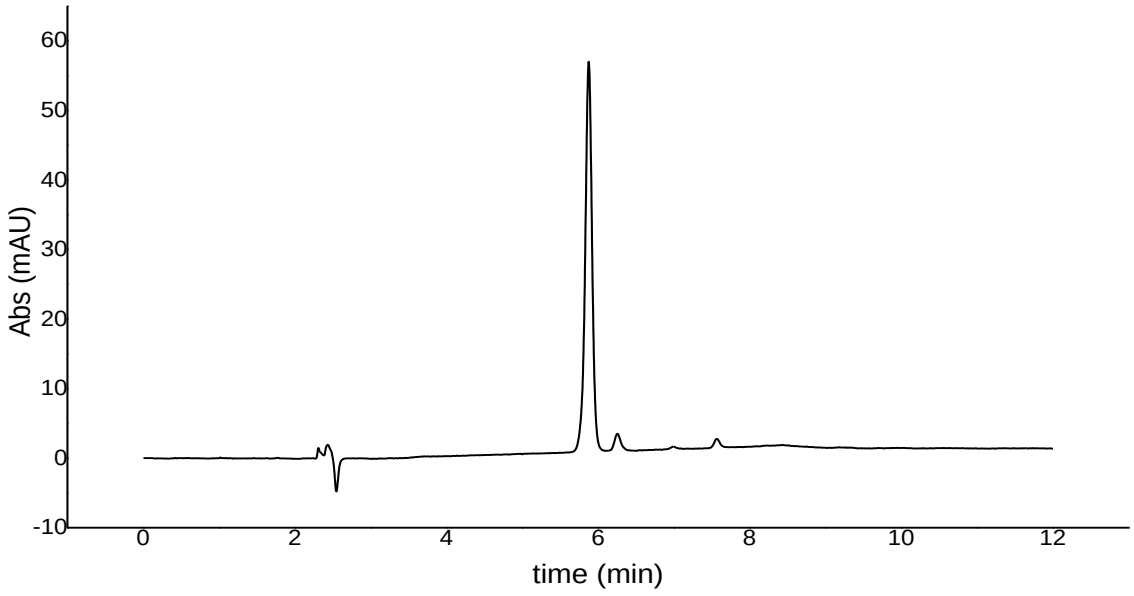
Anexo 56. Chromatogram of ketone **1** synthesized in crude glycerol from corn oil (Cycle 3, 344 nm)



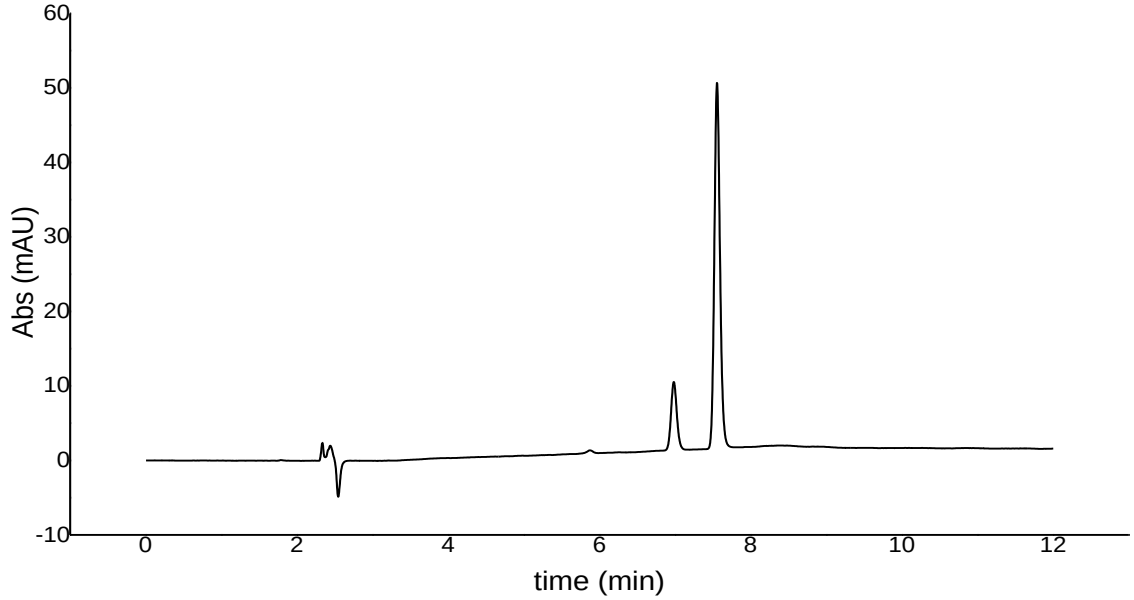
Anexo 57. Chromatogram of ketone **1** synthesized in crude glycerol from corn oil (Cycle 4, 344 nm)



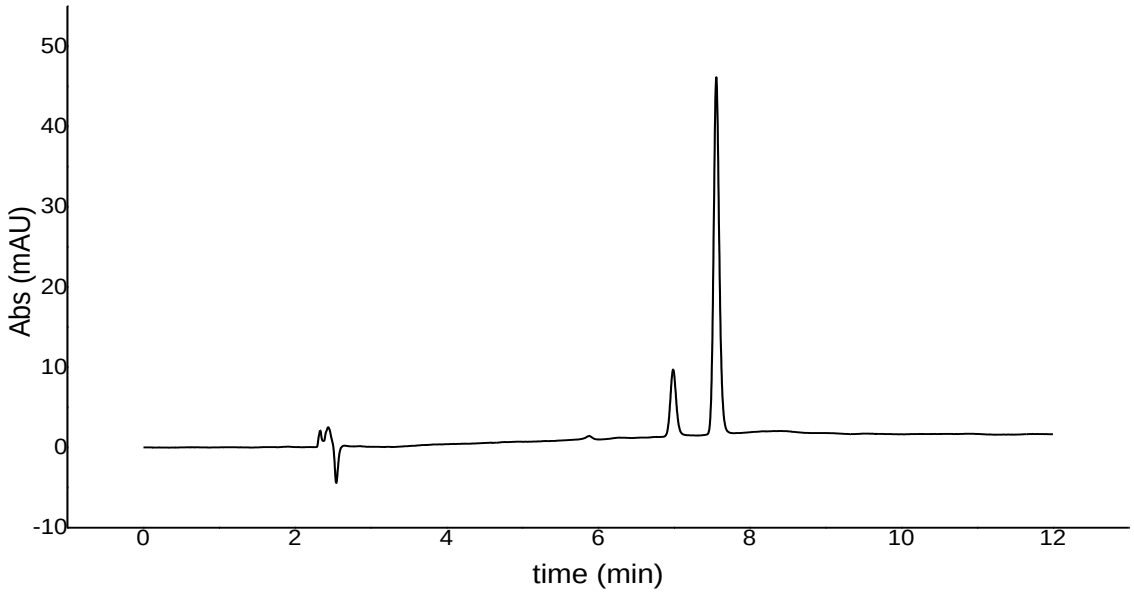
Anexo 58. Chromatogram of ketone **1** synthesized in crude glycerol from corn oil (Cycle 5, 344 nm)



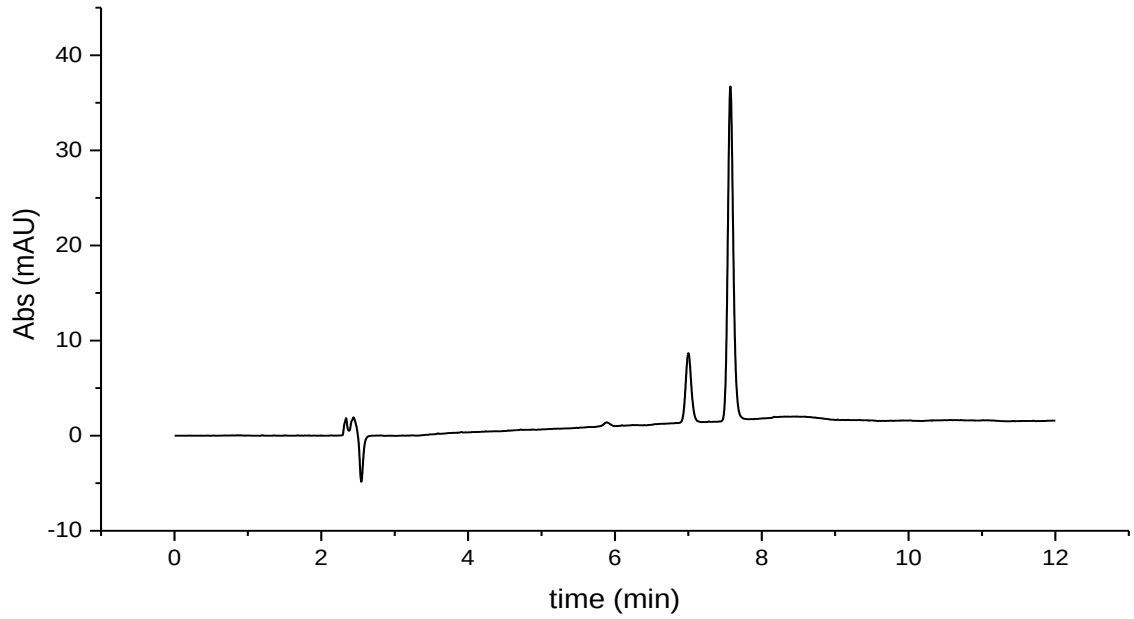
Anexo 59. Chromatogram of ketone **2** synthesized in crude glycerol from sunflower oil (Cycle 1, 328 nm)



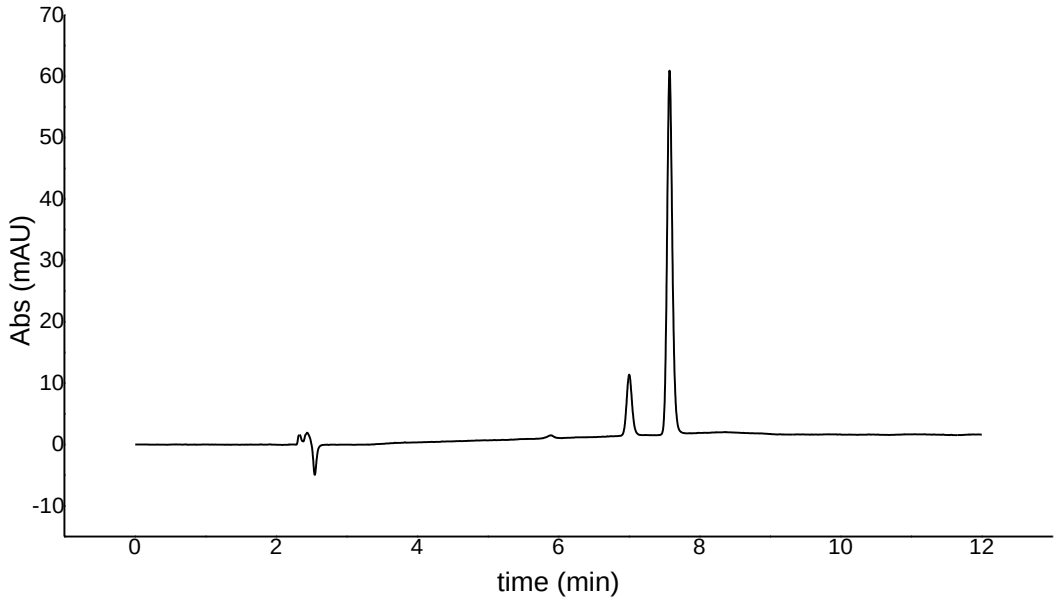
Anexo 60. Chromatogram of ketone **2** synthesized in crude glycerol from sunflower oil (Cycle 2, 328 nm)



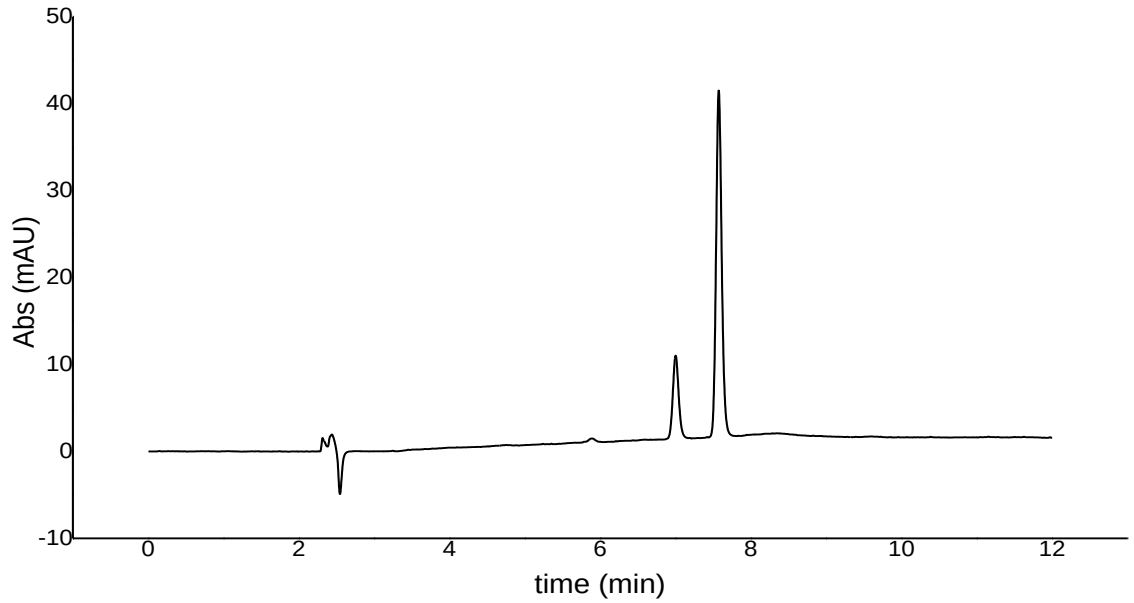
Anexo 61. Chromatogram of ketone **2** synthesized in crude glycerol from sunflower oil (Cycle 3, 328 nm)



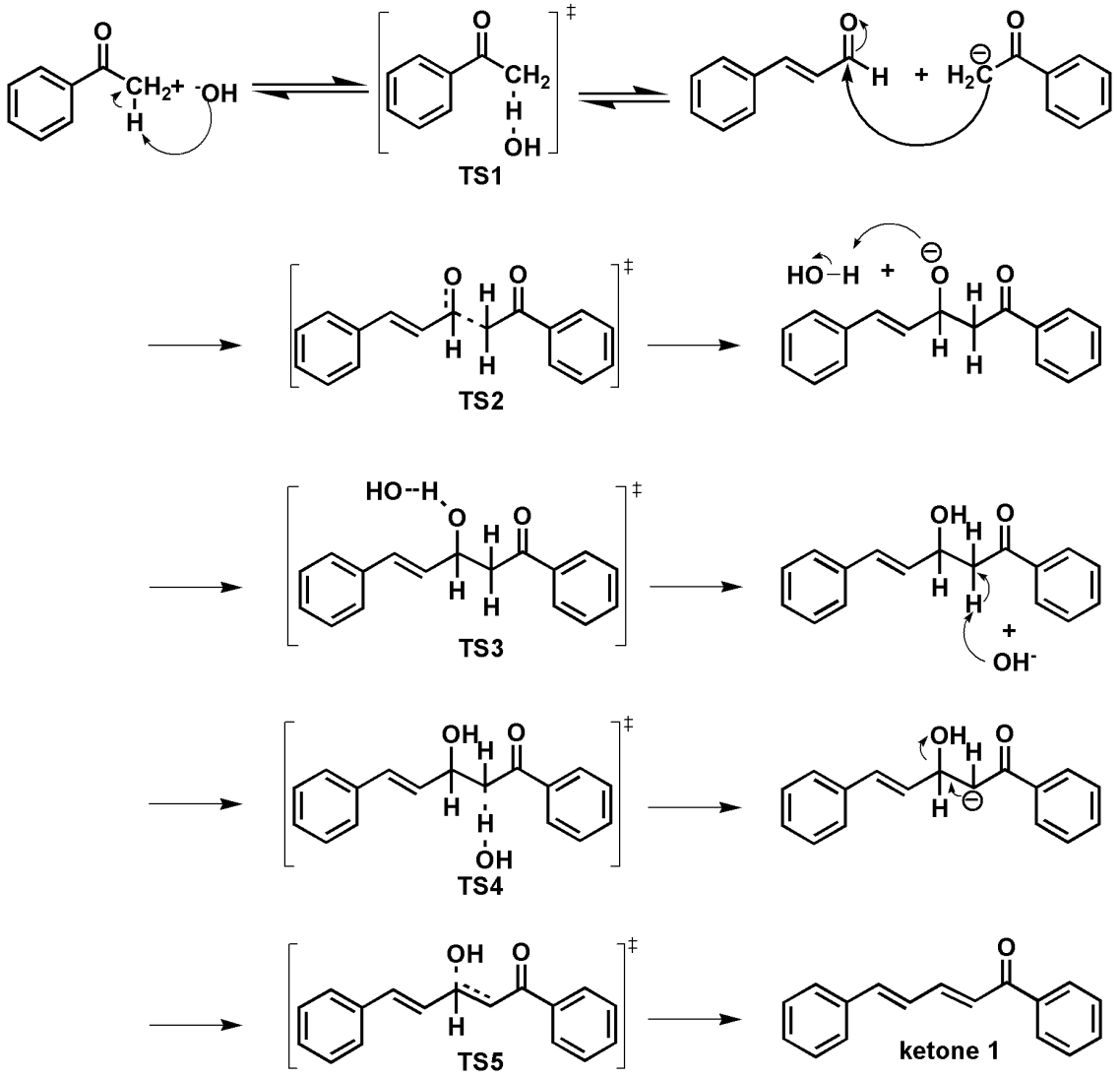
Anexo 62. Chromatogram of ketone **2** synthesized in crude glycerol from sunflower oil (Cycle 4, 328 nm)



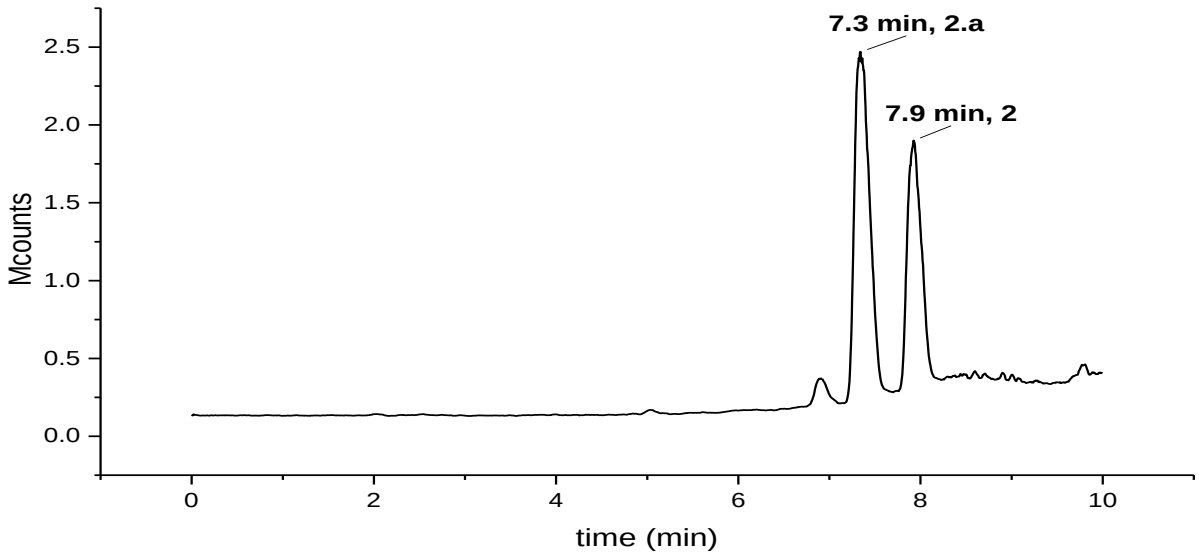
Anexo 63. Chromatogram of ketone **2** synthesized in crude glycerol from sunflower oil (Cycle 5, 328 nm)



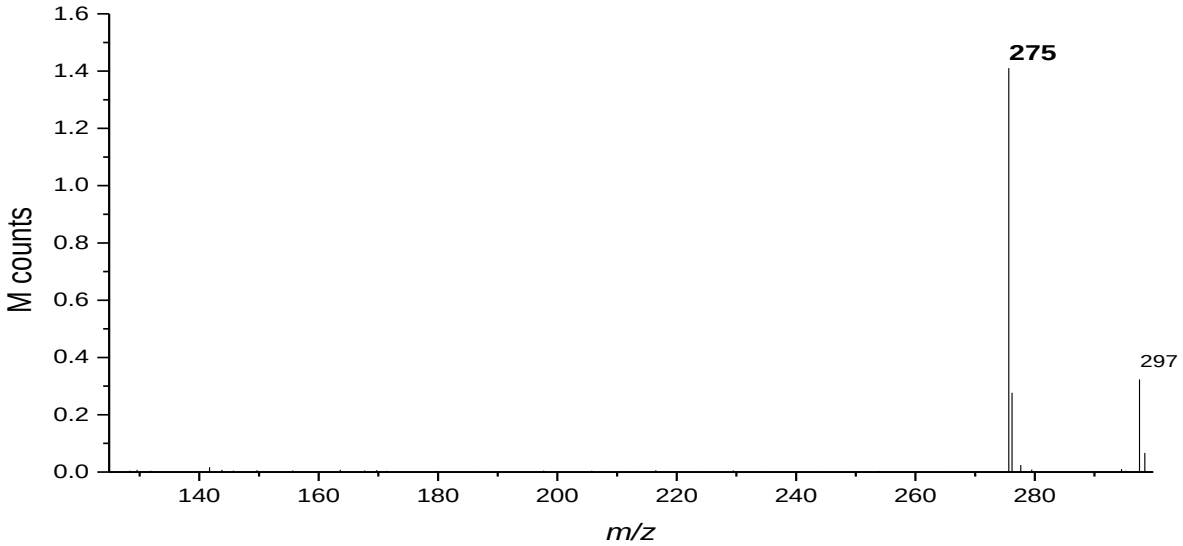
Anexo 64. Proposed mechanism of aldol reaction for synthesis of **1** via carbanion elimination (E1cB)



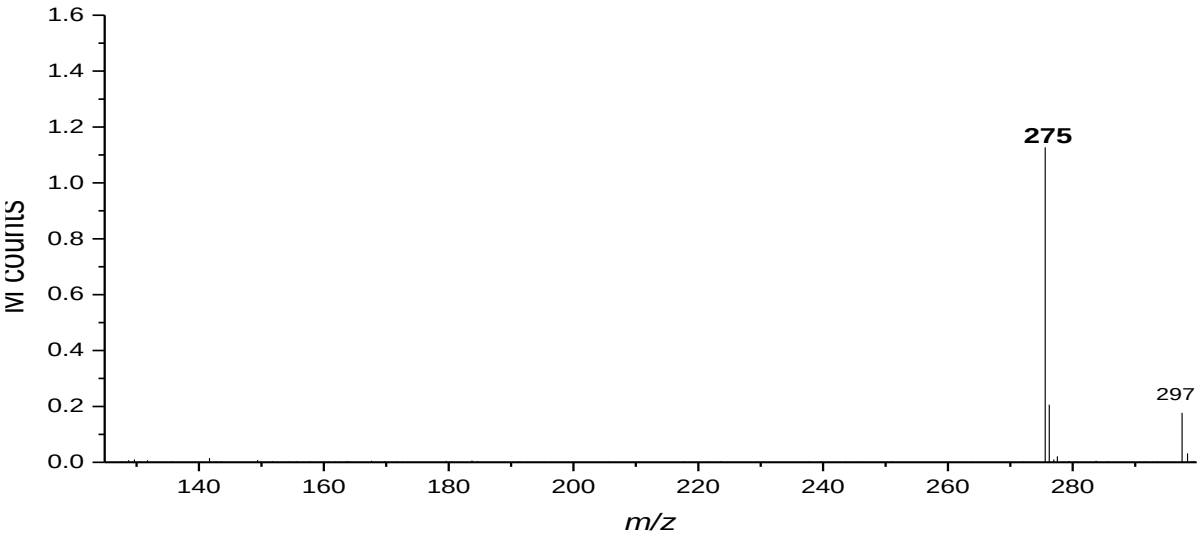
Anexo 65. Chromatogram of ketones **2** and **2.a** from soybean, obtained from HPLC-MS experiment



Anexo 66. Mass Spectrum of ketone **2.a** (*tr* ~ 7.3 min)



Anexo 67. Mass Spectrum of ketone **2** (*tr* ~ 7.9 min)



Anexo 68. UV-Vis spectrum of by-product **2.a** from HPLC-PAD experiment