Electronic Supplementary Information

for

Enzymatic Monoesterification of Symmetric Diols: Restriction of

Molecular Conformations Influences the Selectivity

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Supplementary Information 1

Table S1. Summary of some selected protocols for mono-functionalization of 1,n-diol and issues concerned with the environment.

No	Protocol	Strategy/Catalytic System developed	Remark	Ref.[a]
1	Monosilylation of symmetrical 1,n-primary diols.	A biphasic process was developed for the selective protection of one of two chemically equivalent primary hydroxyl groups in 1,n-diols using t-butyldiphenyl silyl chloride (TBDPSCl) in diisopropyl ethyl amine (DIEA) and dimethyl formamide (DMF). DIEA had limited solubility in DMF and excess DIEA formed a light phase on top of the DMF phase. The unique selectivity under this biphasic condition was believed due to the constant concentration	**Strength.** Selectivity of monosilylation over disilylation is high upto 92 %. **Environment Concern** TBDPSCl is a hygroscopic, fuming and corrosive reagent. It has a high molecular weight as compared to diols, therefore it is used in large quantities. This reaction requires anhydrous atmosphere and all the reagents i.e. DIEA and DMF should be moisture free. After the reaction is completed the reaction mass is quenched in water due to which DMF is wasted and	19

		(16%) of base (DIEA) maintained in the reaction phase (DMF) during silylation.	this is not environmental friendly. The pure product was obtained after column chromatography.	
2	Selective mono protection of diols, diamines, and amino alcohols using cesium bases.	This protocol utilizes the three component coupling of diols, diamines, and amino alcohols using alkyl bromides and carbon disulfide in presence of a cesium base and tetrabutylammonium iodide (TBAI).	**Strength.** Process claims very high yield up to 93% in a short period ranging from 1.6 to 2.5 h. **Environmental Concern.** CS_2 is highly toxic with foul smell. DMF is used as a solvent, solvent recovery remains as a problem.	20
3	Selective Monoacylation of 1,n-diols.	Several 1,n-diols, ranging from 1,2-ethanediol to 1,16-hexadecanediol, were selectively monoacylated by transesterification in ester/octane solvent mixtures catalyzed by strongly acidic ion-exchange resins.	**Strength.** Good selectivity of mono esterification over diester, upto 92 %. **Environment Concern.** The reaction is carried out at high temperature of 100^oC and pH of dowex is strongly acidic. Some labile groups may not sustain at such extreme temperature and pH. Drying of the resin beads requires several days.	21
4	Catalytic monosilylation of 1,2-diols	The selective monosilylation of 1,2-diols catalyzed by dimethyltin dichloride was developed.	**Strength.** Very high selectivity of mono protected diols. The reaction is carried out for very short time that is about 1 h and at RT. **Environment Concern.** Me_2SnCl is toxic and corrosive. triethylsilyl chloride (used as 1.5 equiv) is hygroscopic and corrosive.	22

5	Monosilylation of primary and secondary diols.	Monosilylation of heptane diol was carried out using tert-butyl dimethyl silyl chloride (TBSCl) at RT in hexane/MeCN biphasic solvent system.	It was hypothesized that MeCN can solvate both diol and TBSCl while newly formed mono protected species would preferentially migrate to hexane phase due to difference in partition coefficient of diol and monoprotected product.	23
6	A practical and scalable process to selectively monofunctionalize water-soluble α,ω-diols.	Two chemically equivalent hydroxyl groups of water-soluble α,ω-diols were differentiated with dihydropyran (DHP) using a ~5-fold excess of diol in THF or CH_2Cl_2 in presence of a catalytic amount of p-toluenesulfonic acid (TsOH).	**Strength**. Use of inexpensive DHP source and ease to remove excess water-soluble α,ω-diols and THP ether after deprotection render the process scale-friendly without need of column chromatographic separation. The application of present method was also illustrated in the preparation of heterobifunctional diols and well-defined extended to oligo(ethylene glycol). **Environment Concern.** Not suitable for acidic conditions.	24
7	Highly selective silver (I) oxide mediated monoprotection of symmetrical diols.	Treatment of symmetrical diol with Ag_2O and alkyl halide produced the monoprotected derivative in good to excellent yield.	**Strength.** Very high isolated yields of the mono protected products (upto 93 %). **Environment Concern.** High amount of costly silver oxide is being used in the reaction (1.5 mol equivalent). High amount of diester is formed in some of the cases upto 16 %.	25

| 8 | A remarkably simple process for monoprotecting diols | Lipase from pig pancreas (PPL) has been shown to catalyse selectively the hydrolysis of alkane-1,n-diol bis-acetates into the corresponding monoacetate. | **Strength.** The yields of the isolated products are high (79 -95 %).

Use of Porcine pancreas lipase for the hydrolysis of the diester which is environmentally benign process.

Environment Concern. Initially bis acetates are prepared and then hydrolysis of one ester is carried out.

Preparation of diester with acetic anhydride requires anhydrous and moisture free reaction condition.

The hydrolysis of the diester is carried out at pH 6.9 which is maintained by addition of aq. NaOH solution periodically.

The pure product is obtained after column chromatography. | 26 |

a. The reference numbers are in context with the main text in the manuscript.

Table S2. The proportion of monoester mixed with diester (of But-2-yne-1,4-diol and Heptanoic acid) and the signal (4.23:4.64) ratio.

	Monoester spiked with % of diester	The ratio of signal at 4.23 and 4.64
1	0	0.89
2	25	0.65
3	50	0.42
4	75	0.20
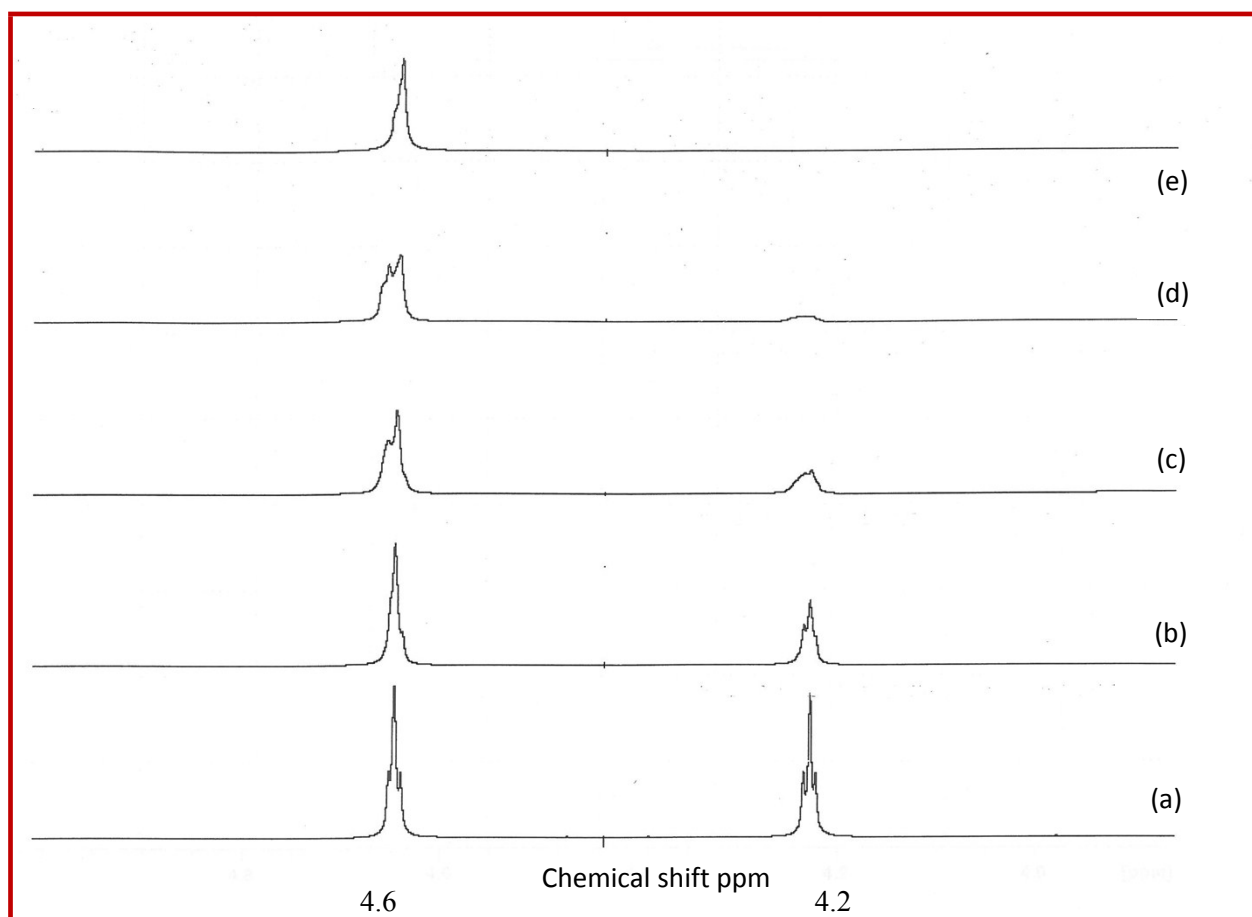
Fig. S1. Variation in ^{1}HNMR signal intensity with changing the proportion of monoester and diester (of But-2-yne-1,4-diol and Heptanoic acid) in a mixture. (a) 100 % Monoester (b) 25 % Diester + 75 % Monoester (c) 50 % Diester + 50% Monoester (d) 75 % Diester + 25% Monoester (e) 100 % Diester.

A graph of % of spiked diester and the peak ratio was drawn.
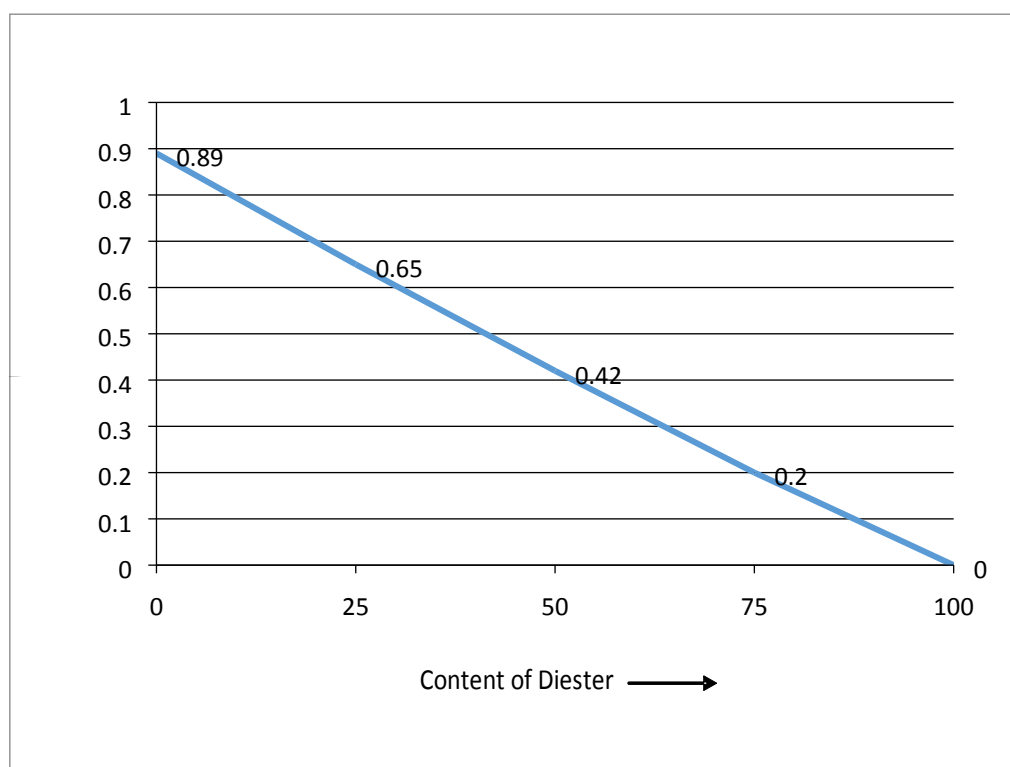
Fig. S2. Calibration curve to calculate the monoester to diester ratio in reaction mixture.

Calculation of slope

Slope = y2-y1/x2-x1

= 0.65 – 0.42 / 25 - 50

= - 0.0092

Using the slope the content of mono ester and diester can be calculated for any unknown sample.

Content of diester when the ratio of peak at 4.23 and 4.64 is about 0.65

X = y-c / m

= 0.65 – 0.89 / - 0.0092

= 26 %

Table S3. pKa values of carboxylic acids with different chain length.[1]

Acid	pKa value
Benzoic acid	4.2
Formic acid	3.75
Acetic acid	4.76
Propionic acid	4.86
Butyric acid	4.83
Pentanoic acid	4.84
Hexanoic acid	4.85
Heptanoic acid	4.89
Octanoic acid	4.89
Nonanoic acid	4.96

1. D. D. Perrin, B. Dempsey and E. P. Serjeant, pKa Prediction for Organic Acids and Bases, Springer, 1981.
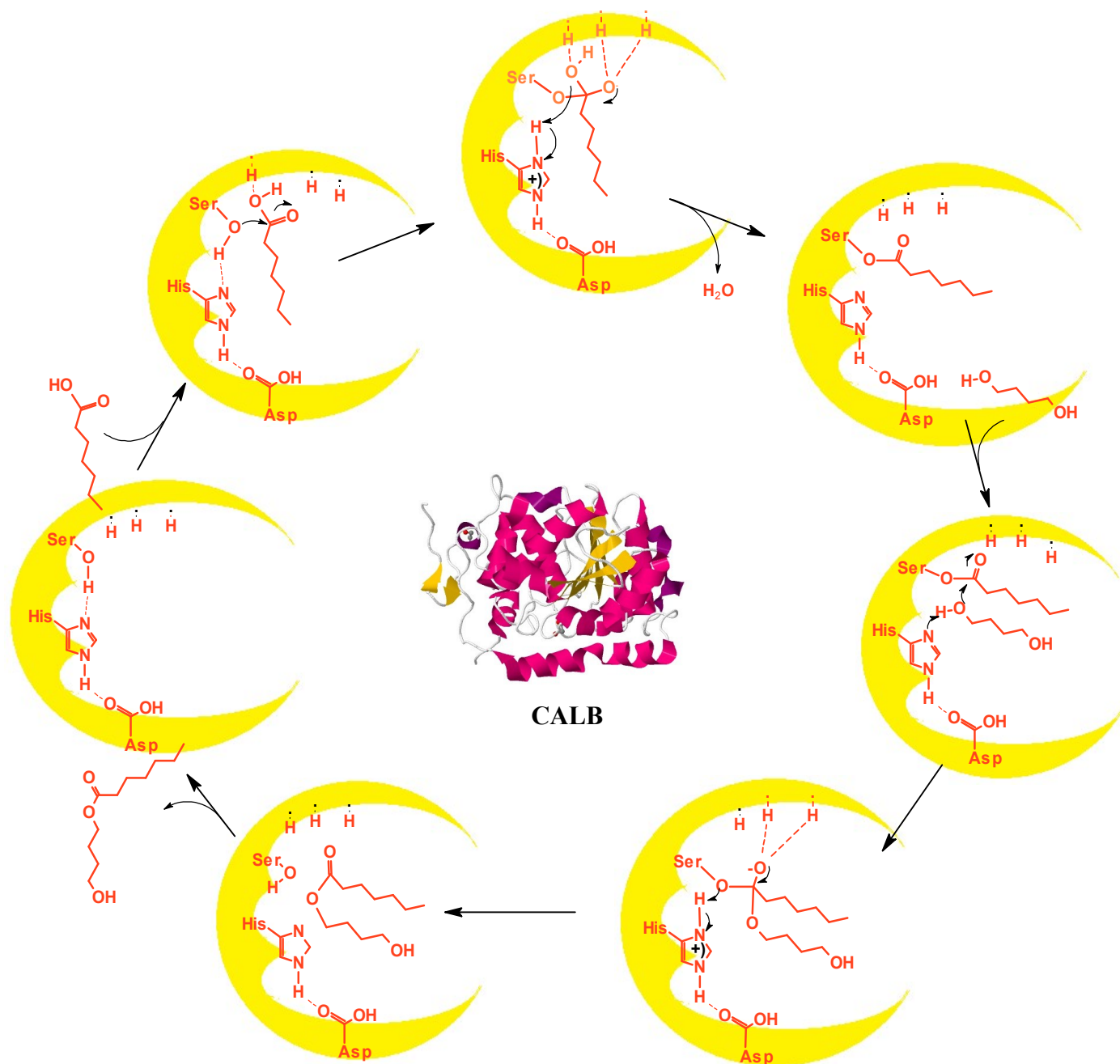
Scheme S1. Proposed mechanism of enzymatic esterification of symmetrical diol in the enzymatic groove. (The same kind of mechanism is discussed in reference 44 i.e S. Sen and J. E. Puskas, *Molecules,* 2015, **20**, 9358-9379 but for transesterification of vinyl acetate with 2-phenylpropane-1-ol).
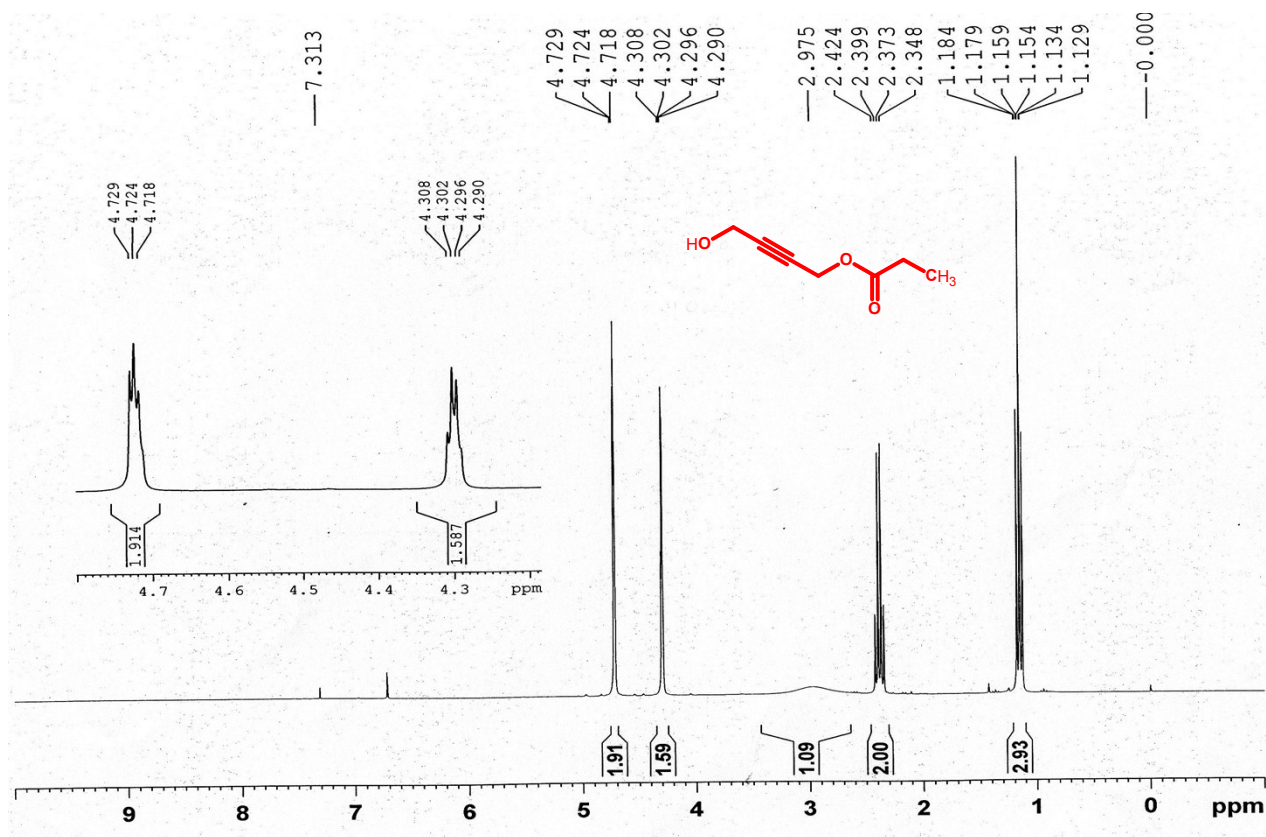
Figure S1. 1HNMR spectrum of 4-hydroxybut-2-yn-1-yl propanoate.
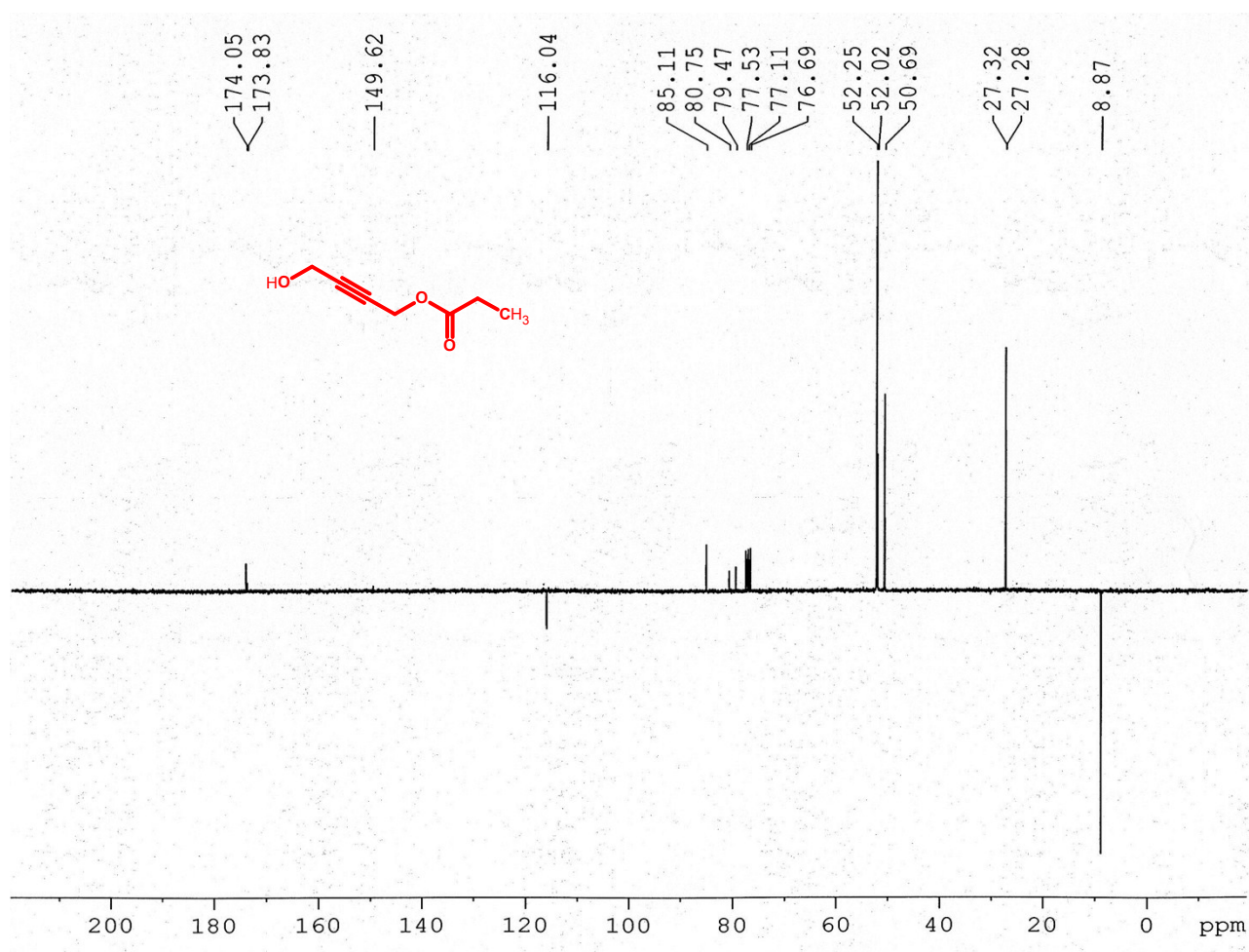
Figure S2. APT of 4-hydroxybut-2-yn-1-yl propanoate.
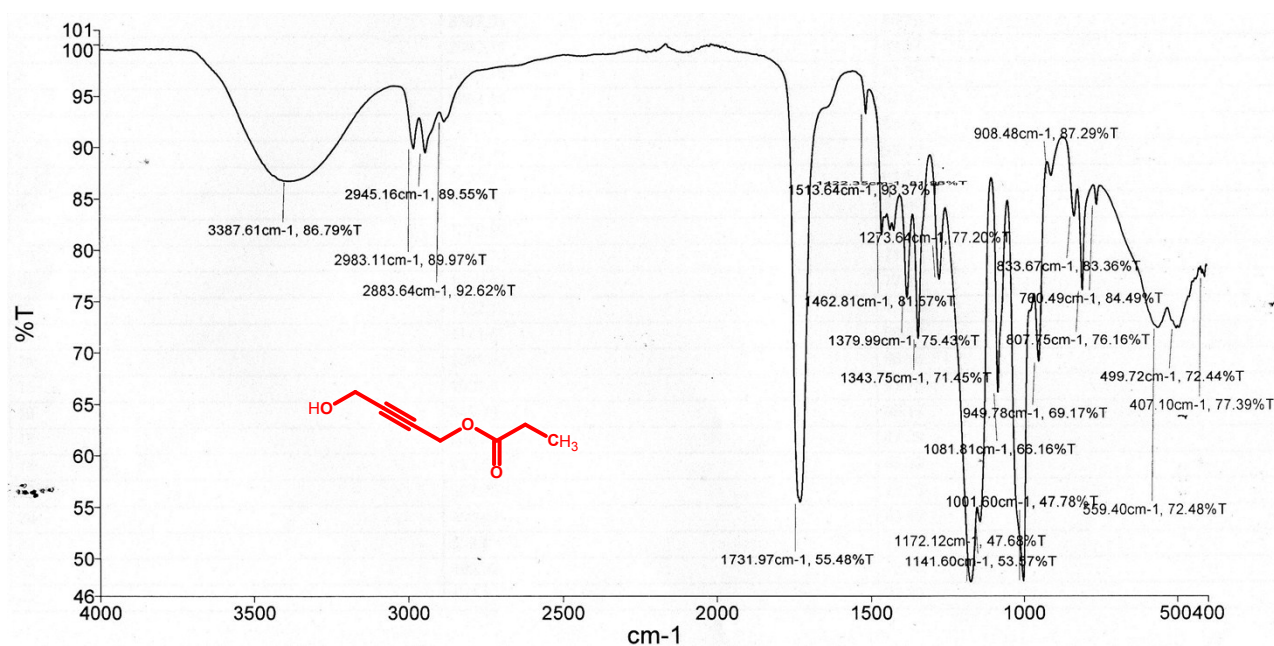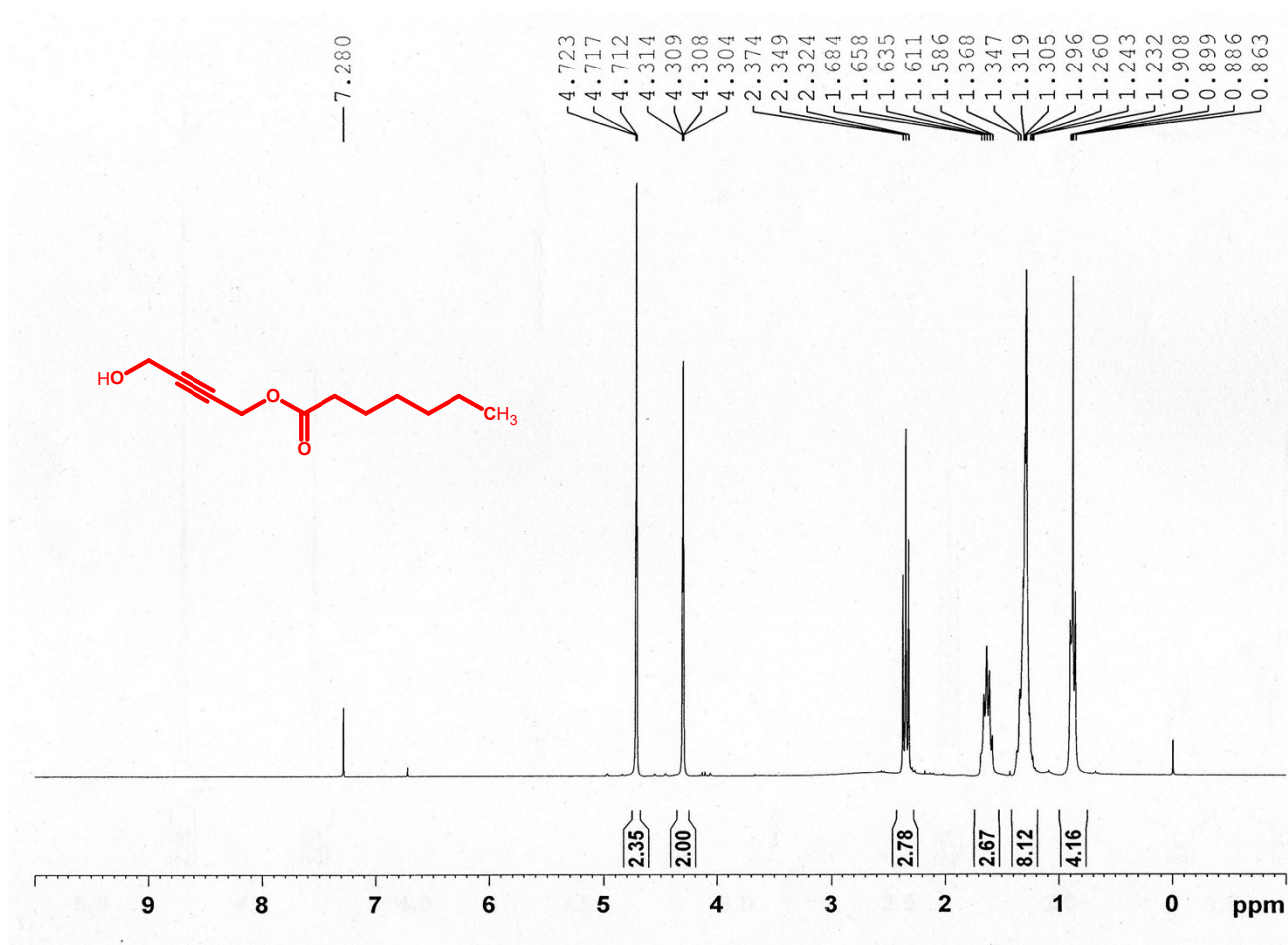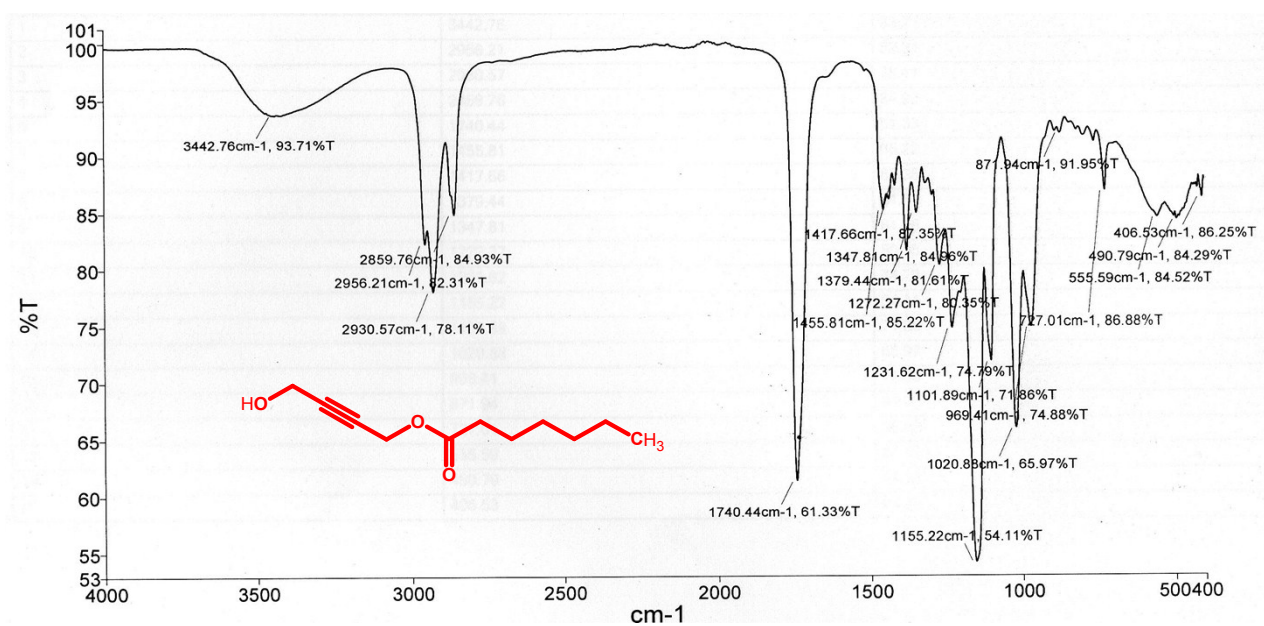
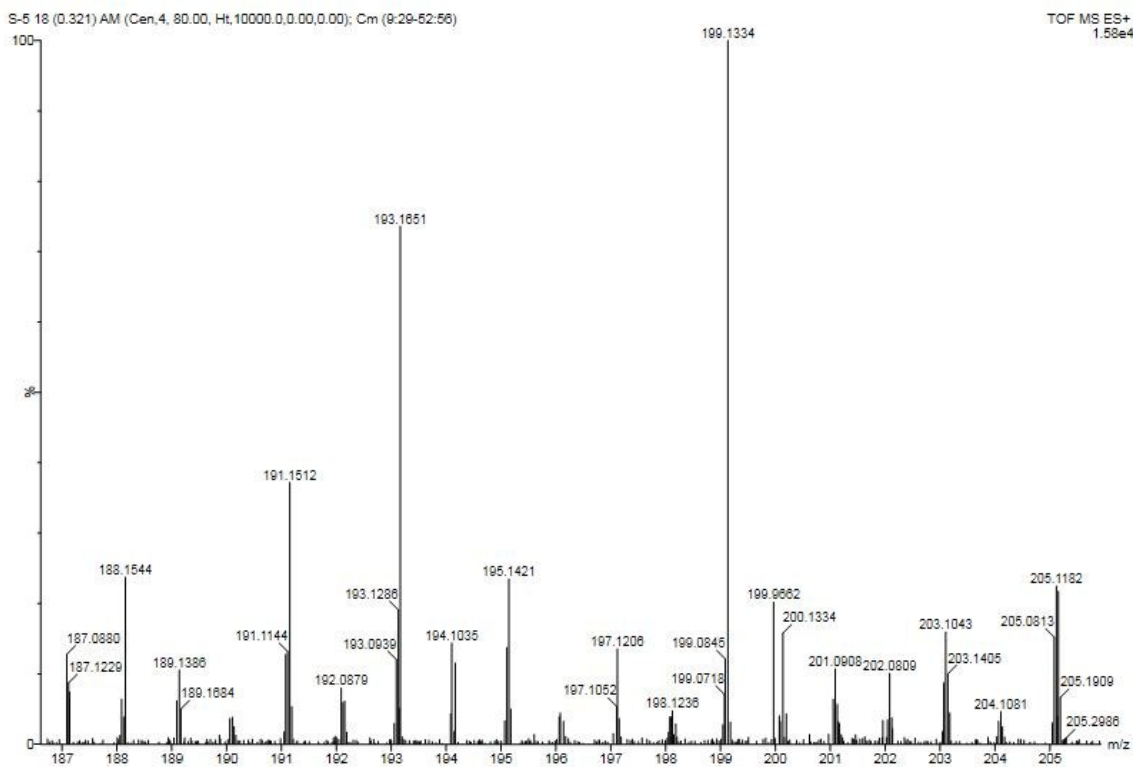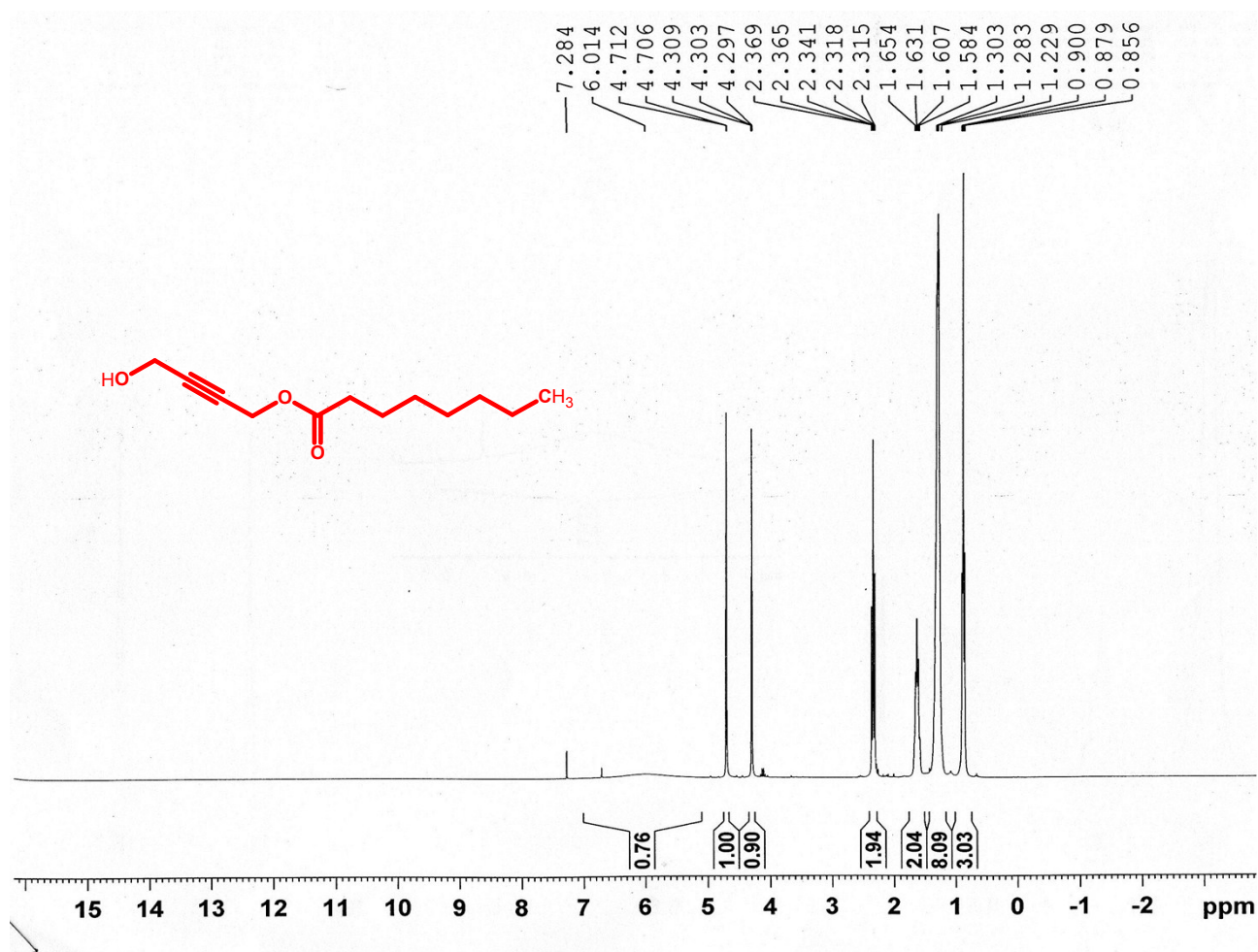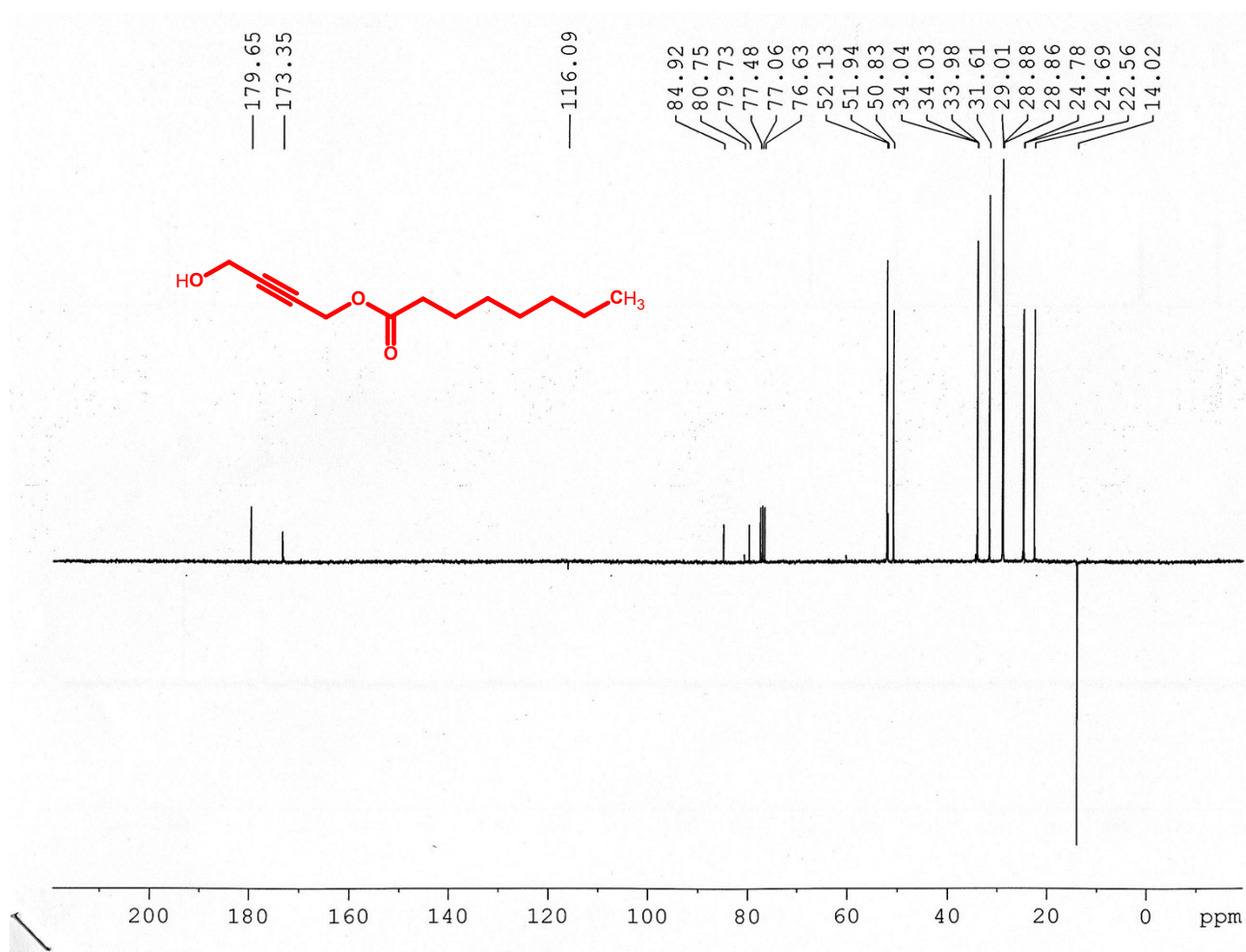**Figure S3. FTIR spectrum of 4-hydroxybut-2-yn-1-yl propanoate.**
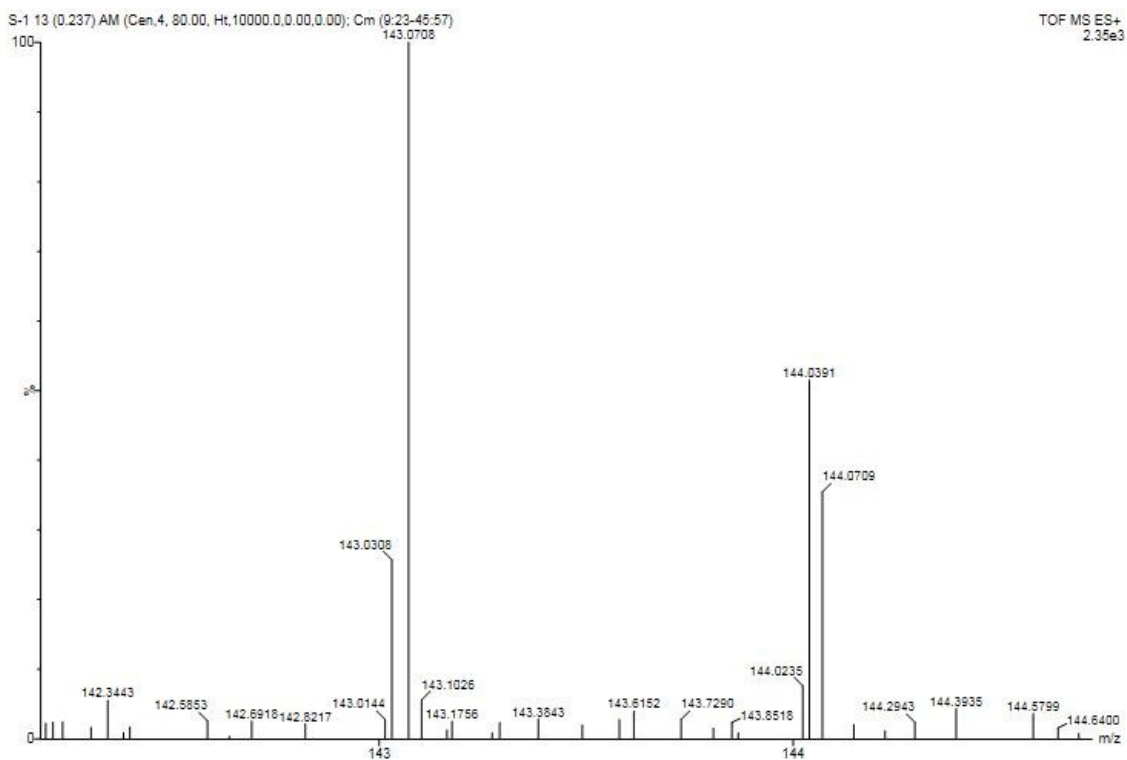
Figure S4. HRMS of 4-hydroxybut-2-yn-1-yl propanoate.
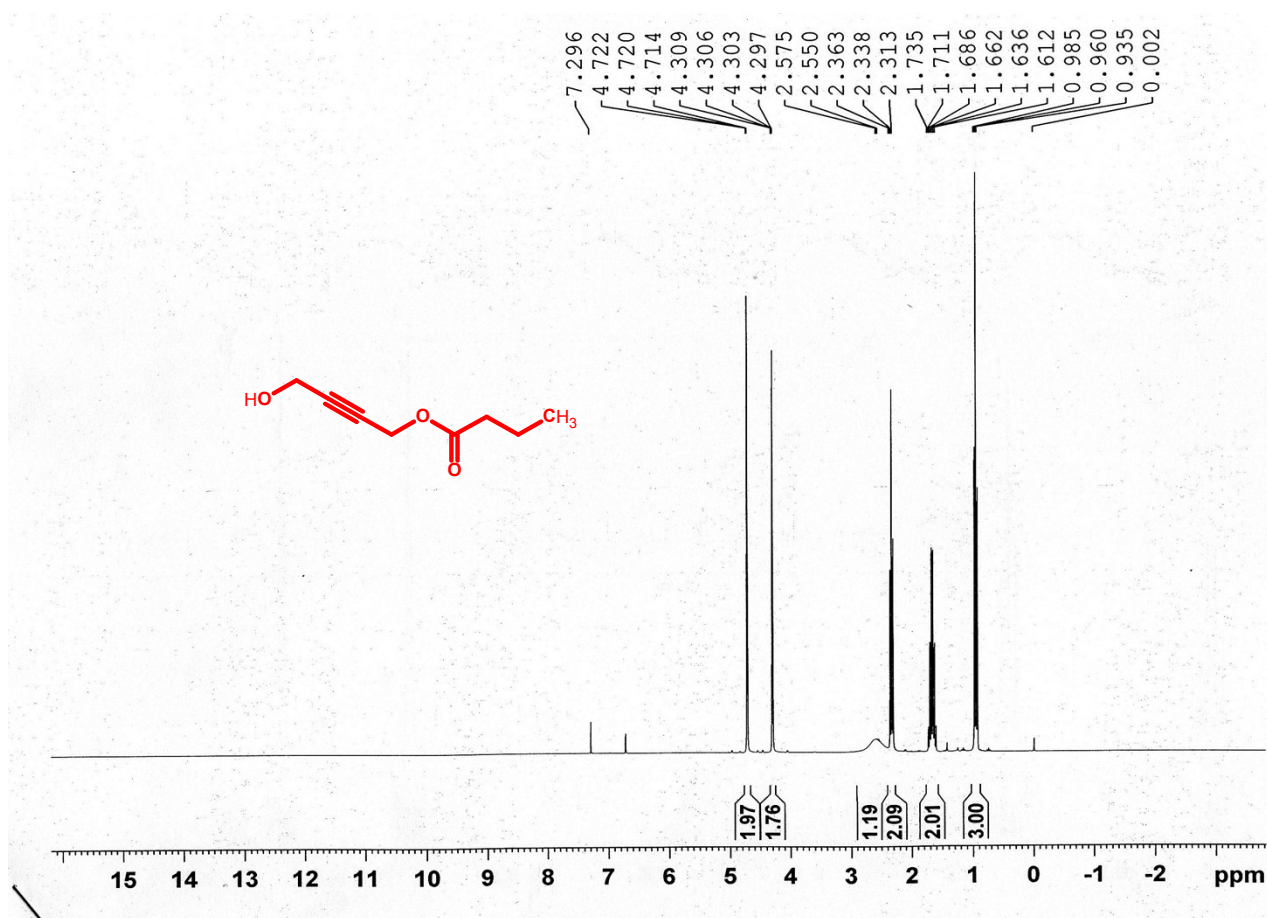
Figure S5. 1HNMR spectrum of 4-hydroxybut-2-yn-1-yl butanoate.
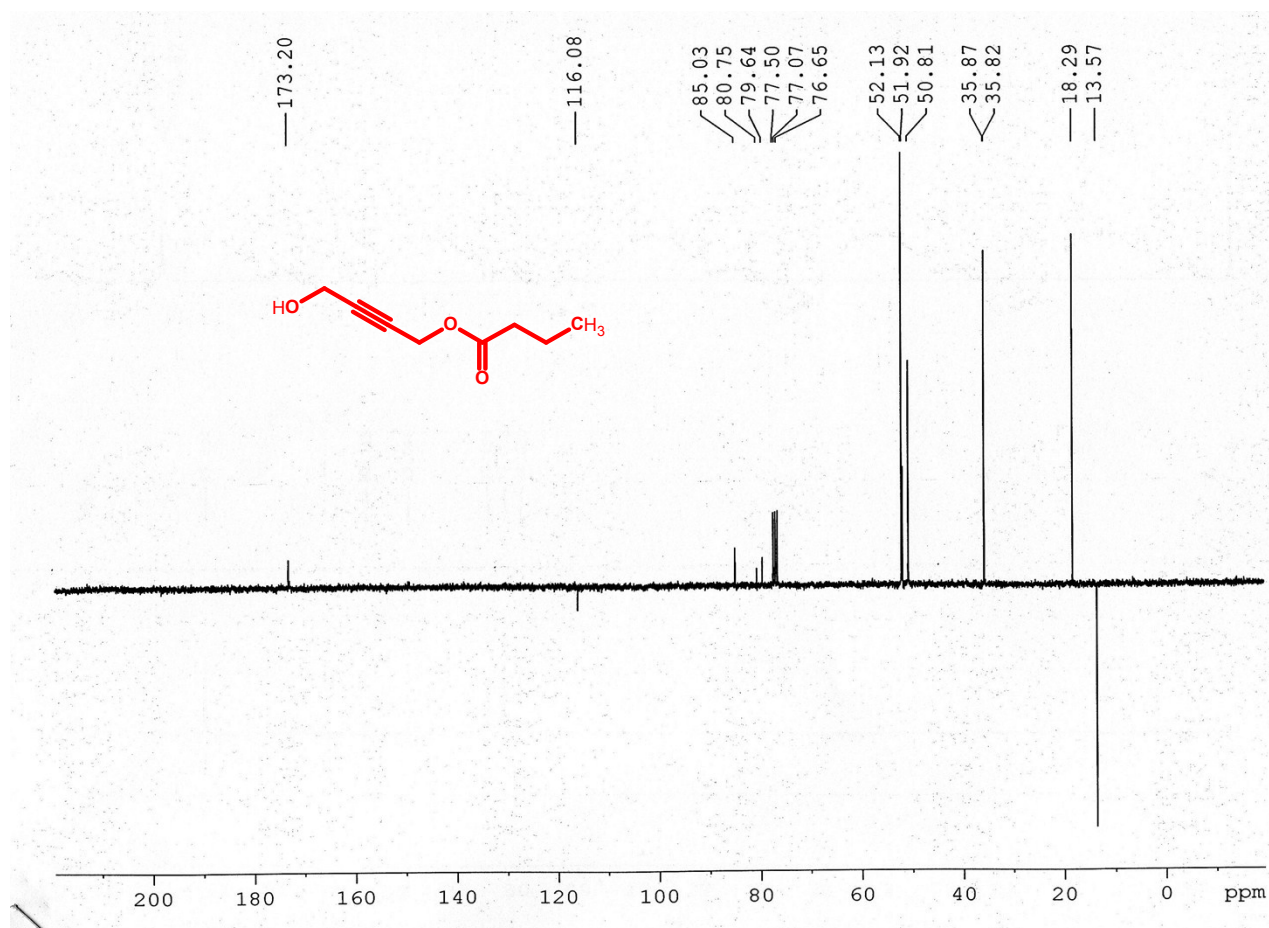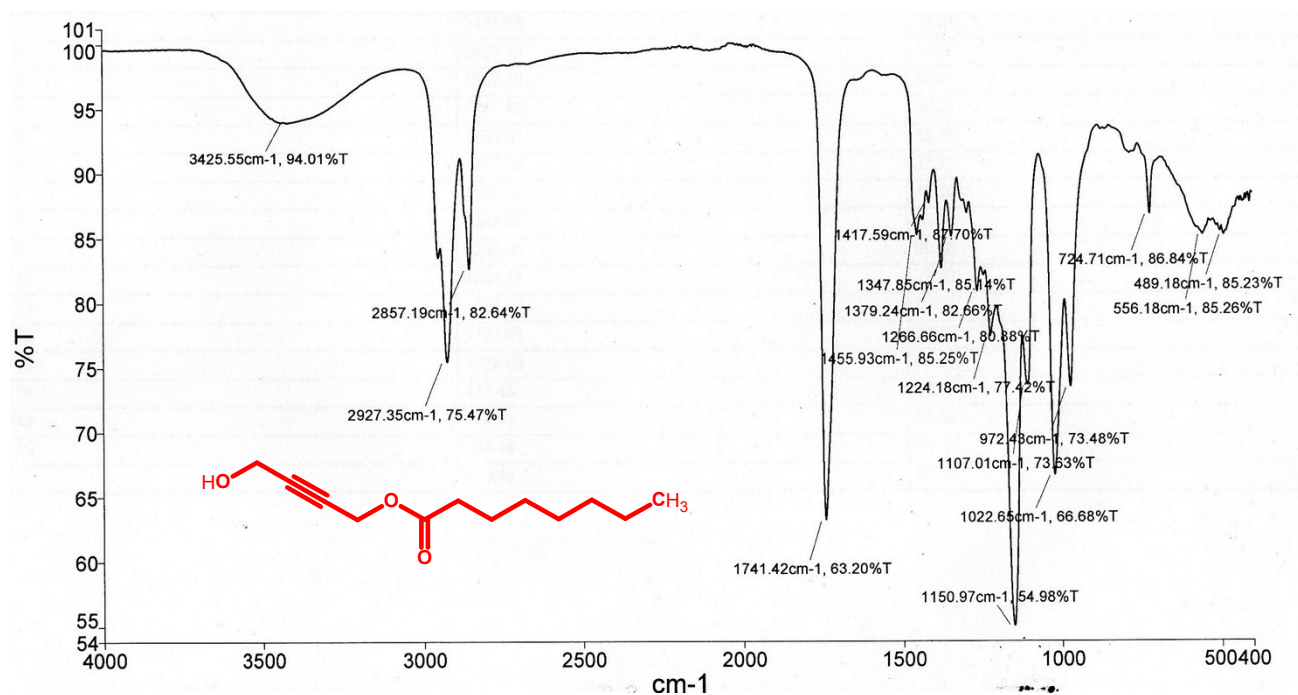
Figure S6. APT of 4-hydroxybut-2-yn-1-yl butanoate.
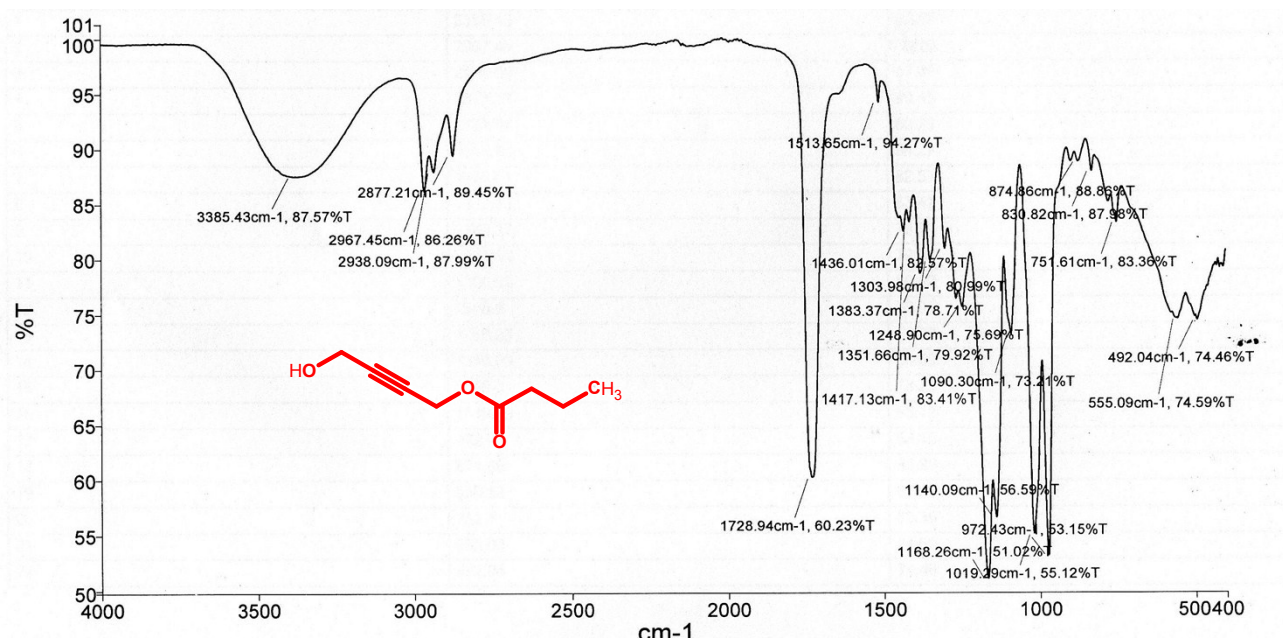
Figure S7. FTIR spectrum of 4-hydroxybut-2-yn-1-yl butanoate.
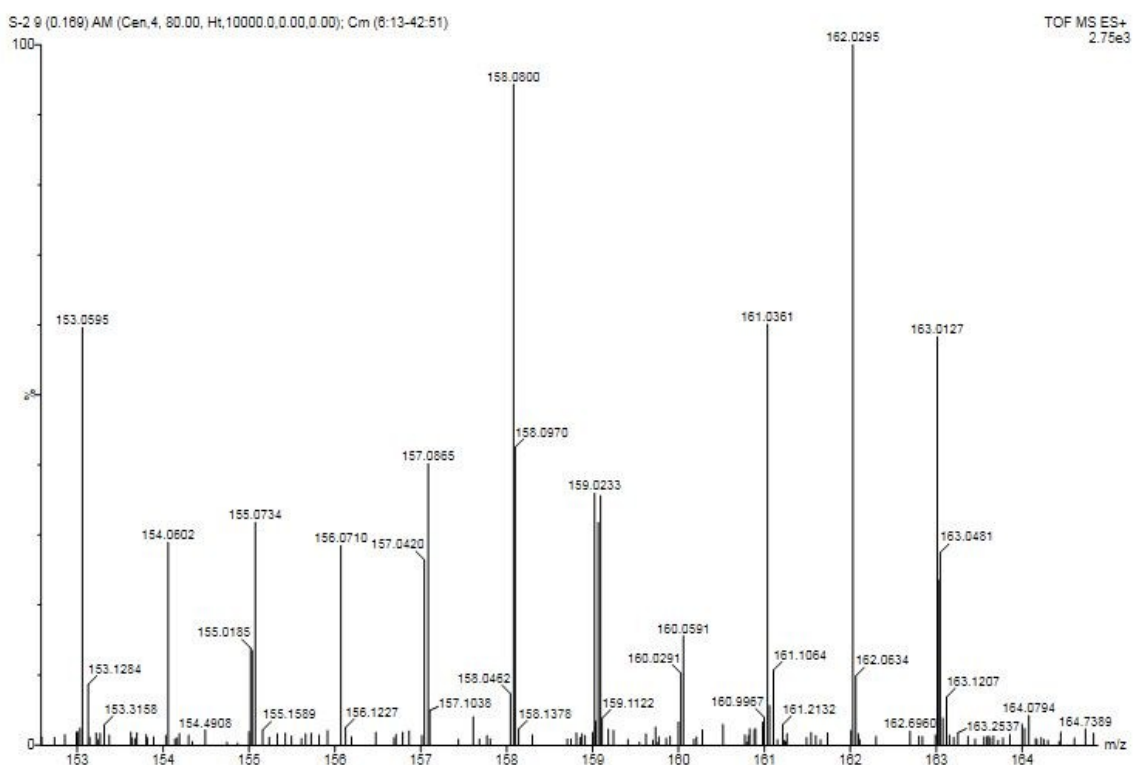
Figure S8. HRMS spectra of 4-hydroxybut-2-yn-1-yl butanoate.
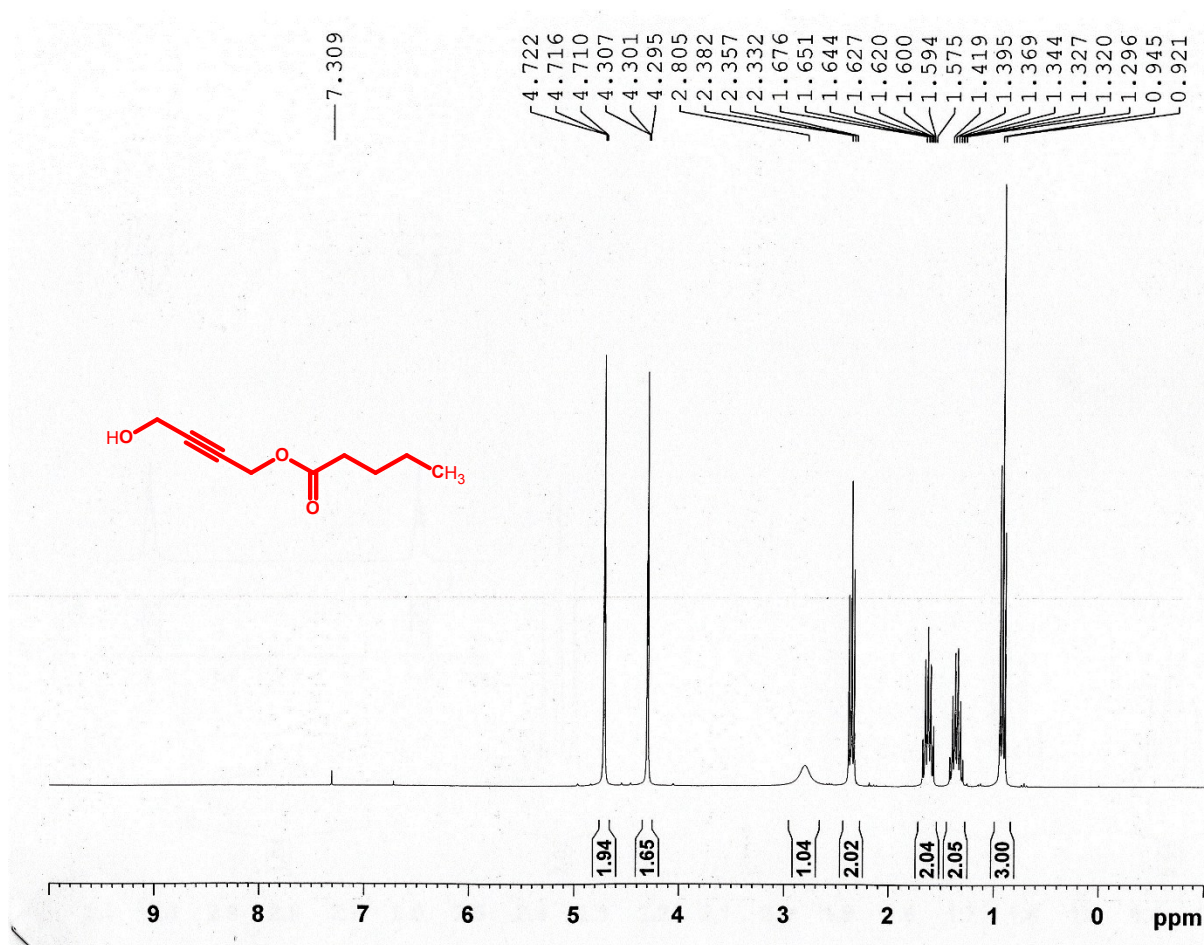
Figure S9. 1HNMR spectrum of 4-hydroxybut-2-yn-1-yl pentanoate.
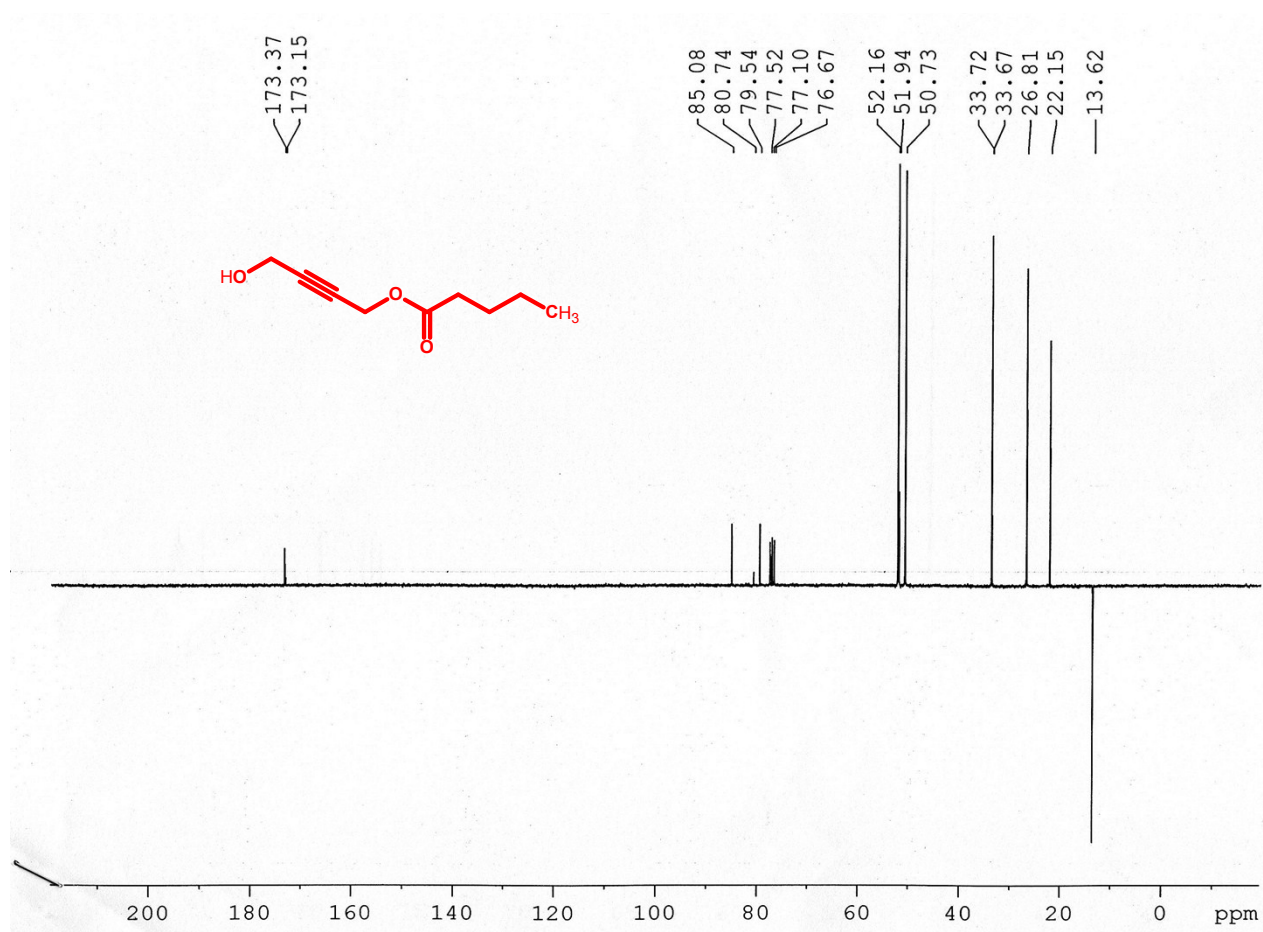
Figure S10. APT of 4-hydroxybut-2-yn-1-yl pentanoate.
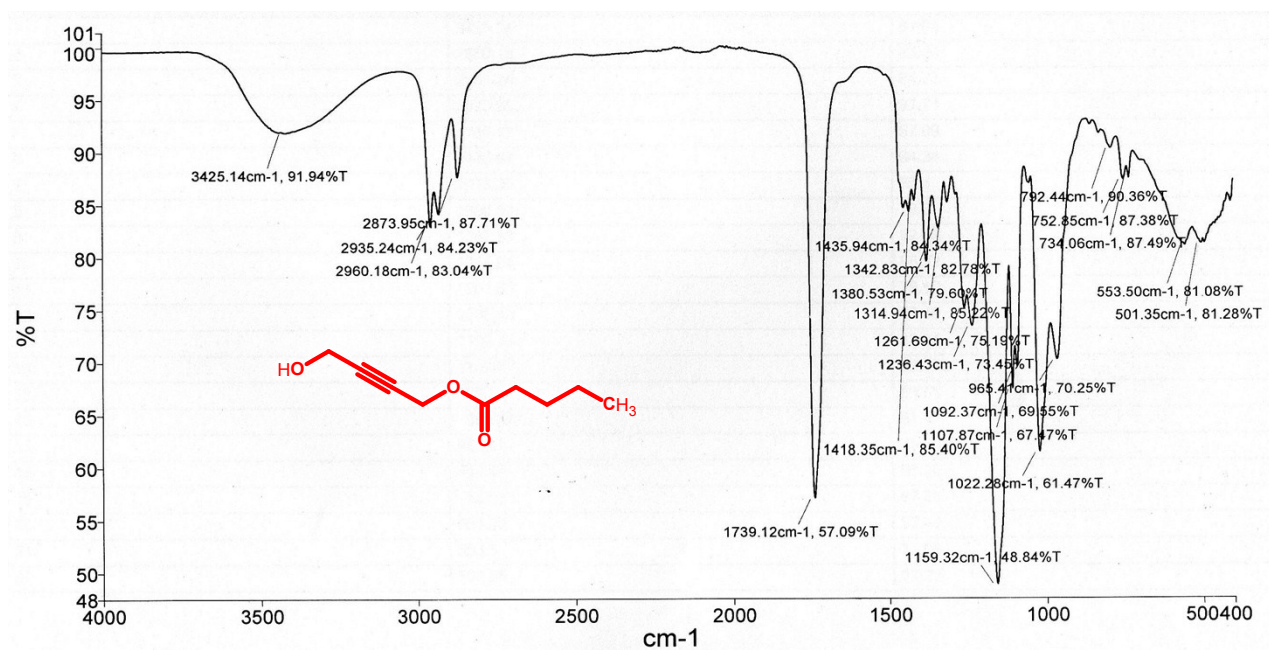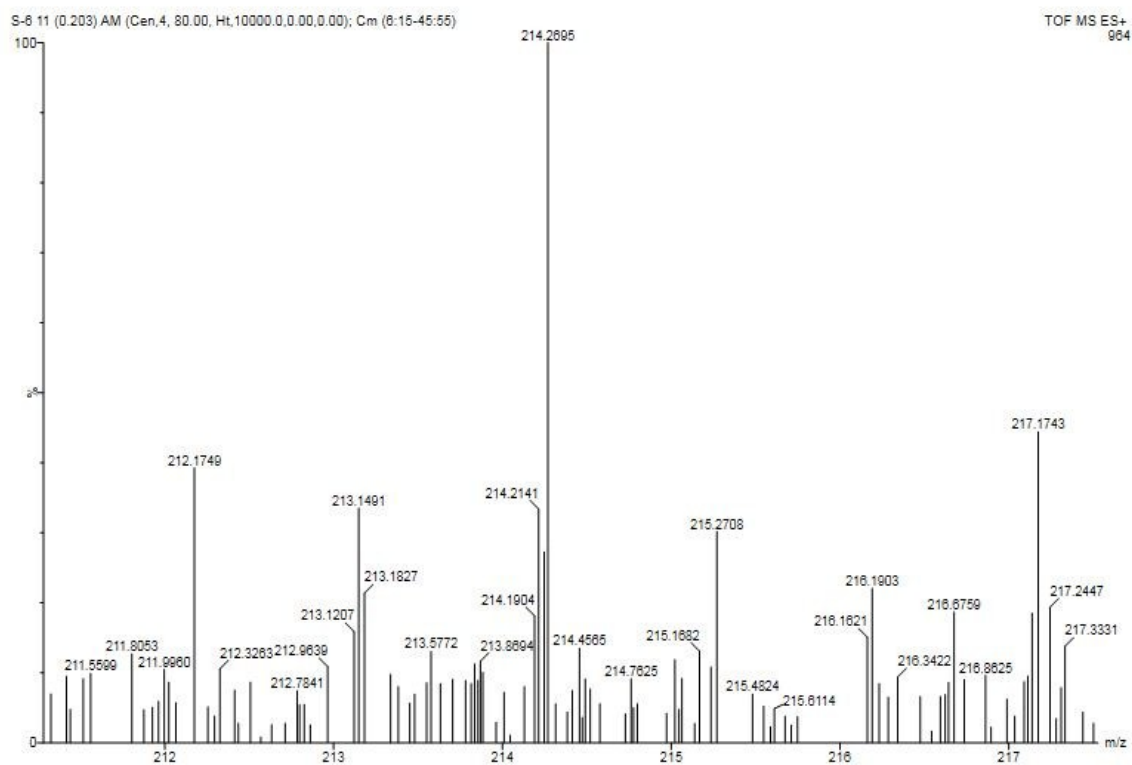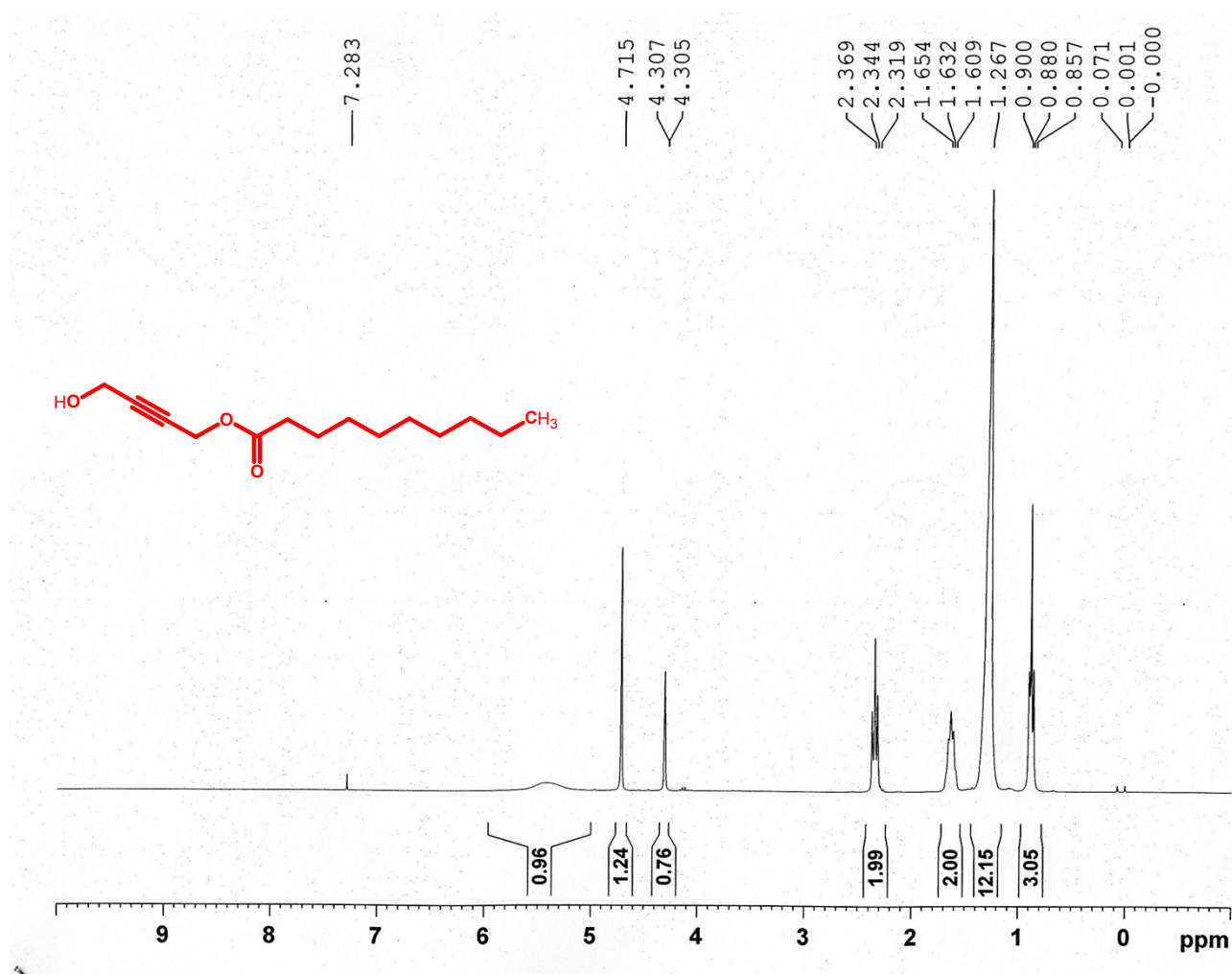
Figure S11. FTIR spectrum of 4-hydroxybut-2-yn-1-yl pentanoate.
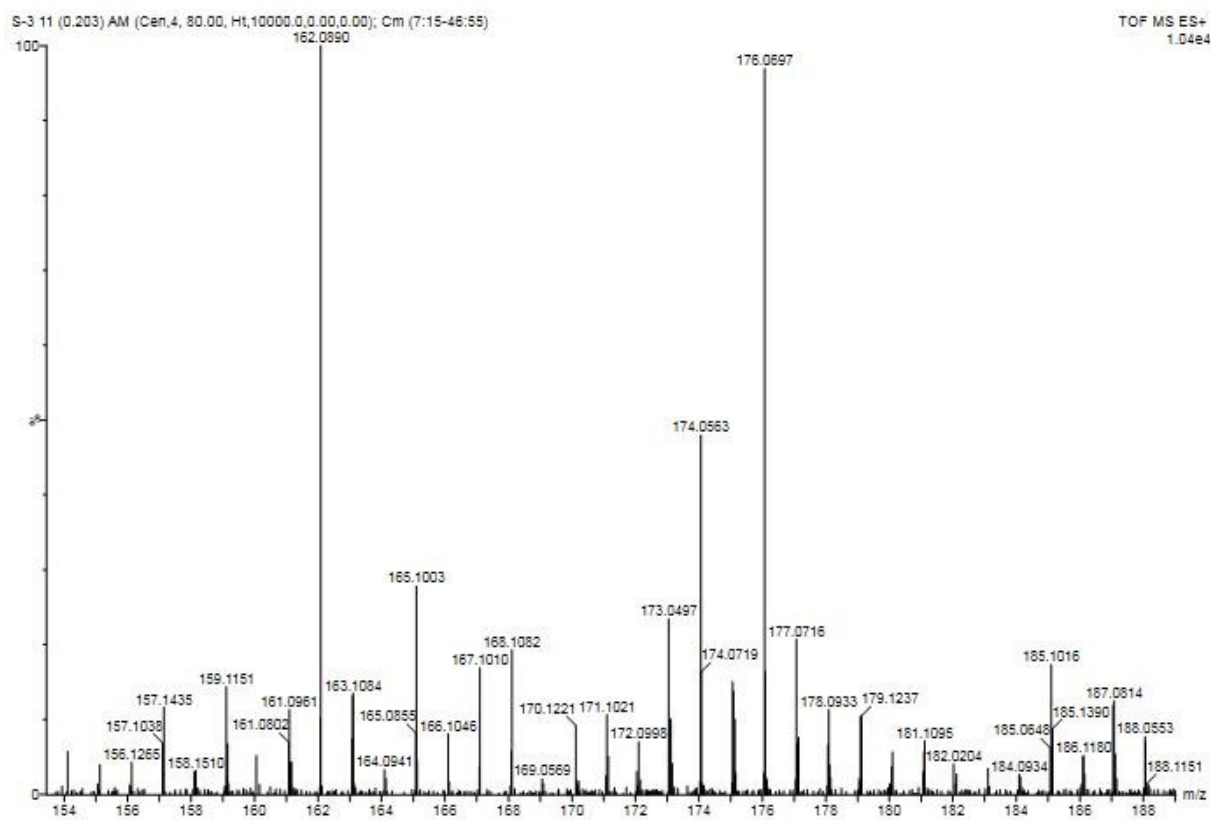
Figure S12. HRMS spectra of 4-hydroxybut-2-yn-1-yl pentanoate.
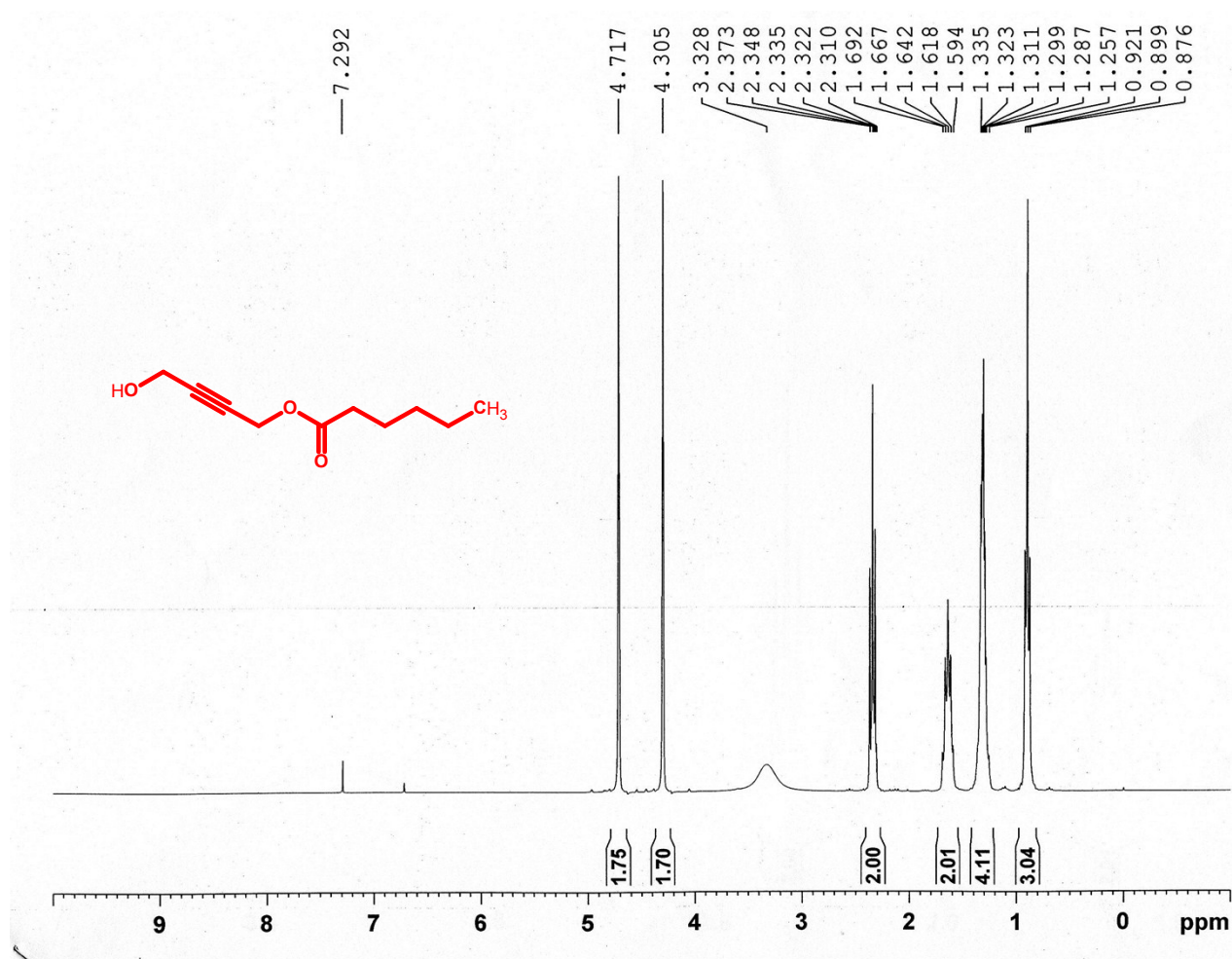
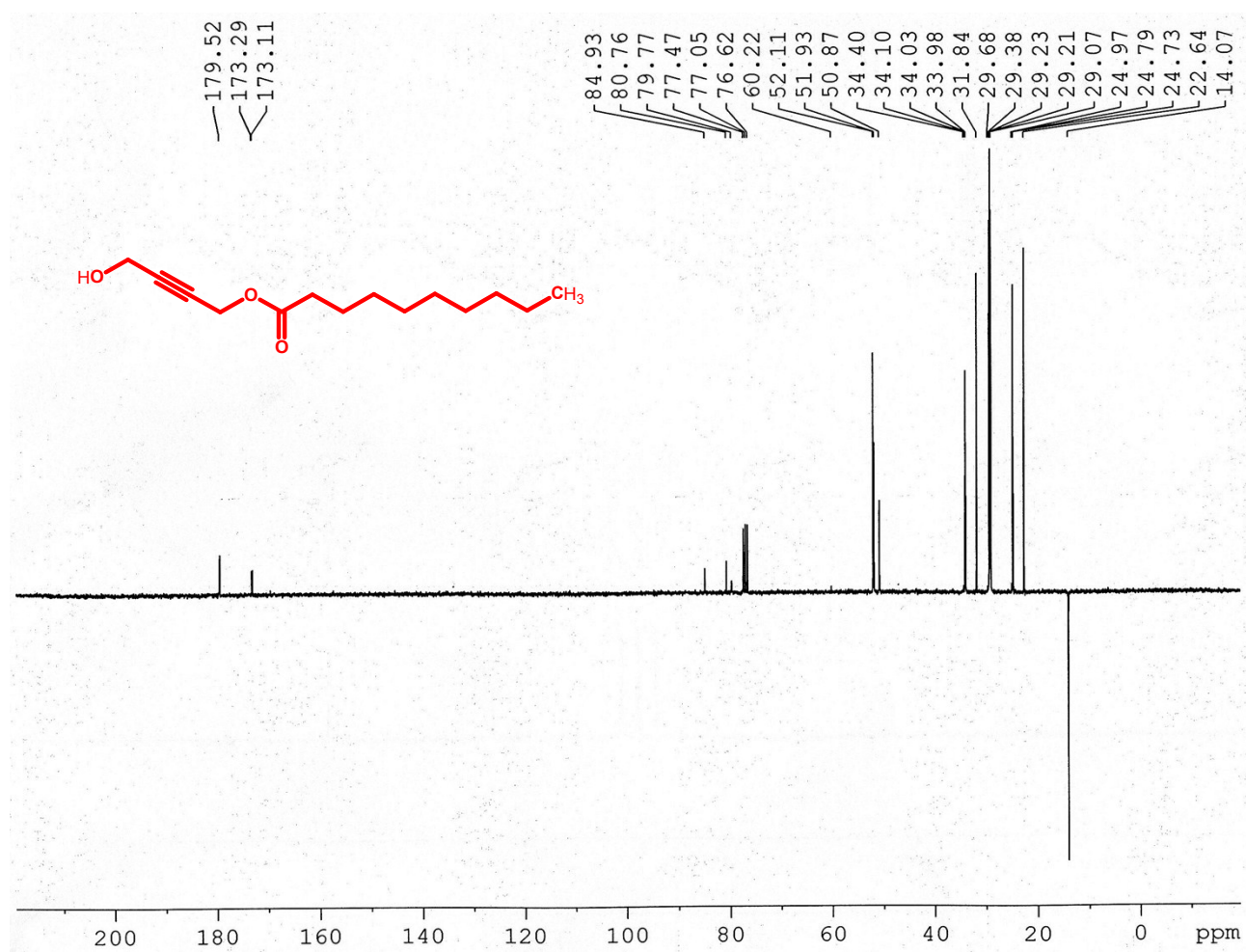**Figure S13. 1HNMR spectrum of 4-hydroxybut-2-yn-1-yl hexanoate.**
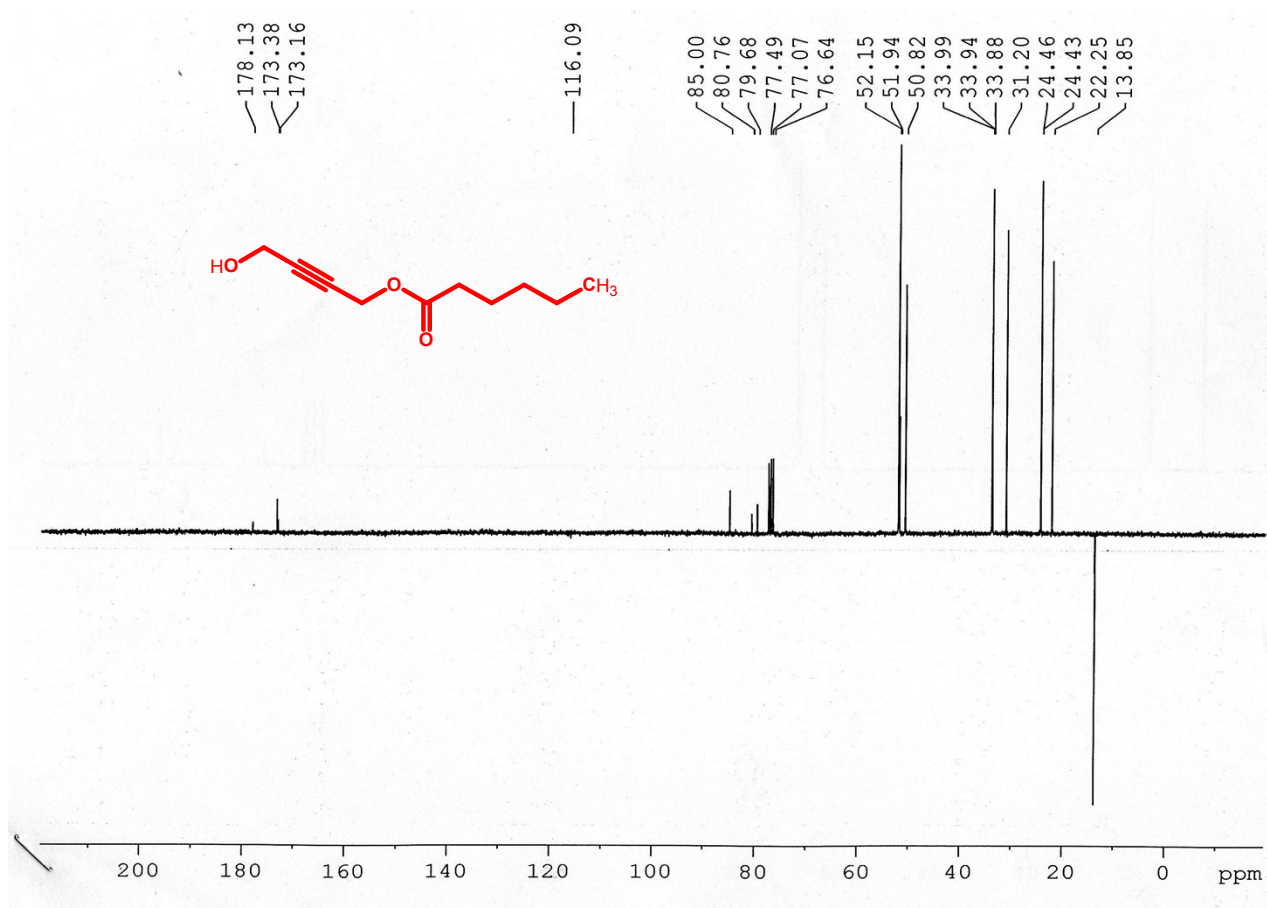
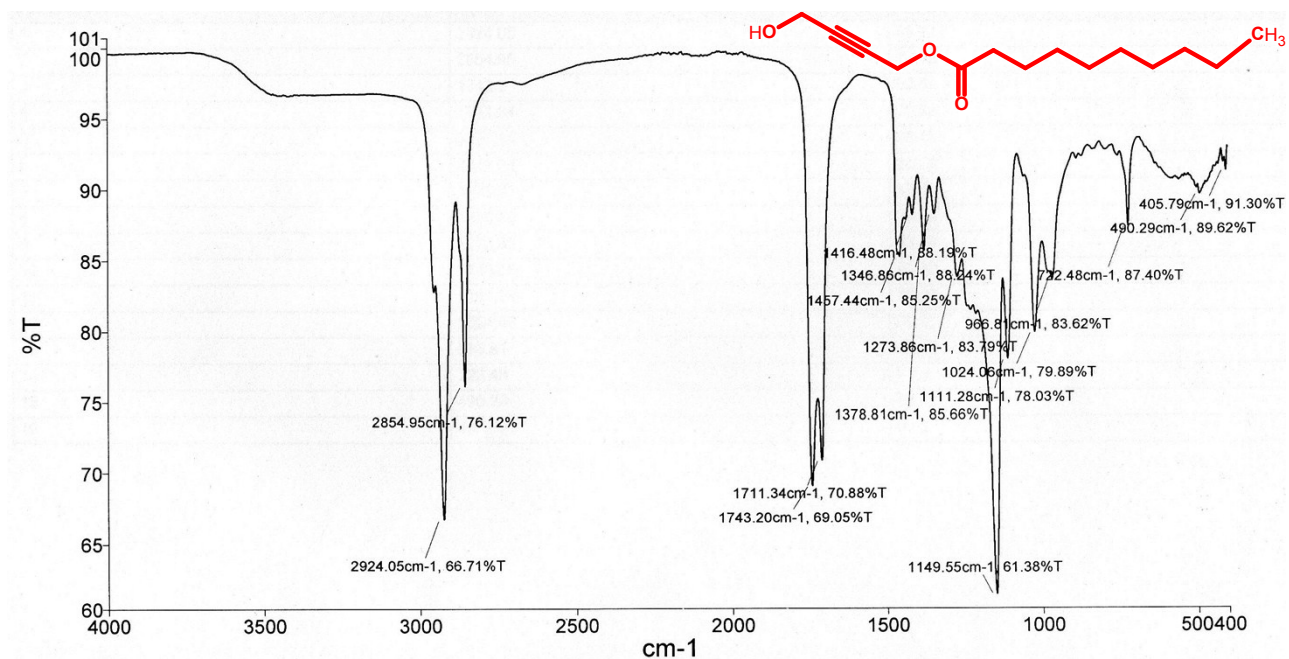Figure S14. APT of 4-hydroxybut-2-yn-1-yl hexanoate.
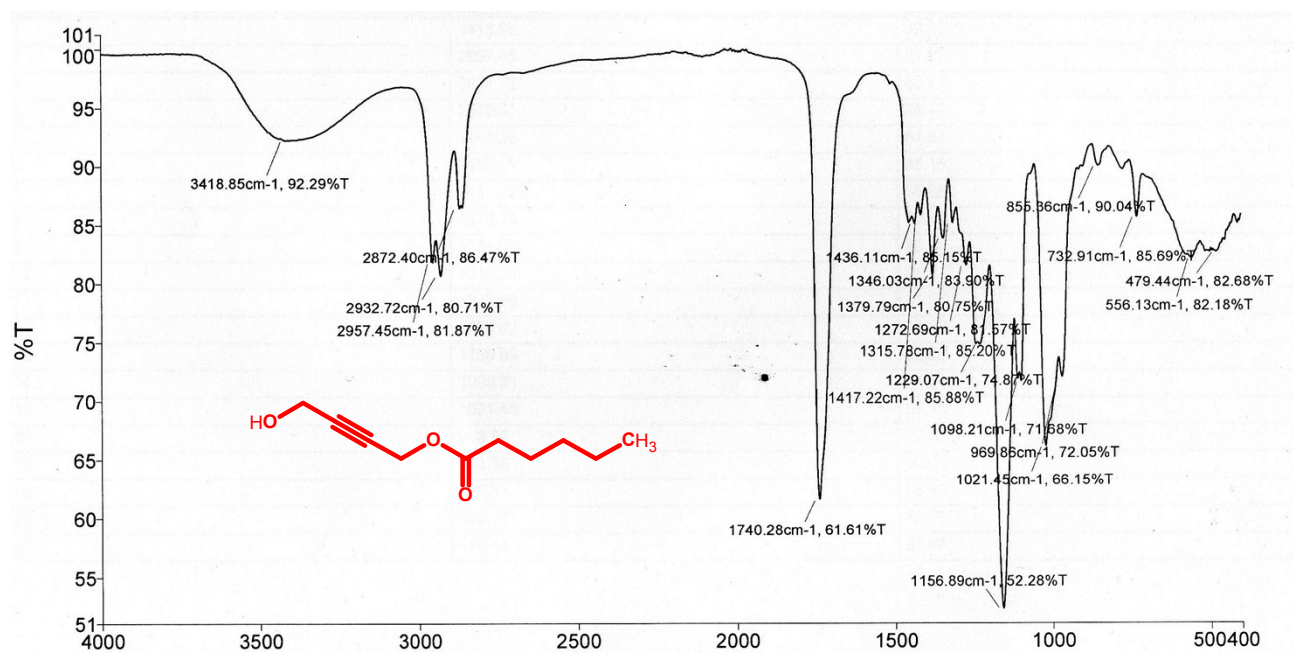
Figure S15. FTIR spectrum of 4-hydroxybut-2-yn-1-yl hexanoate.
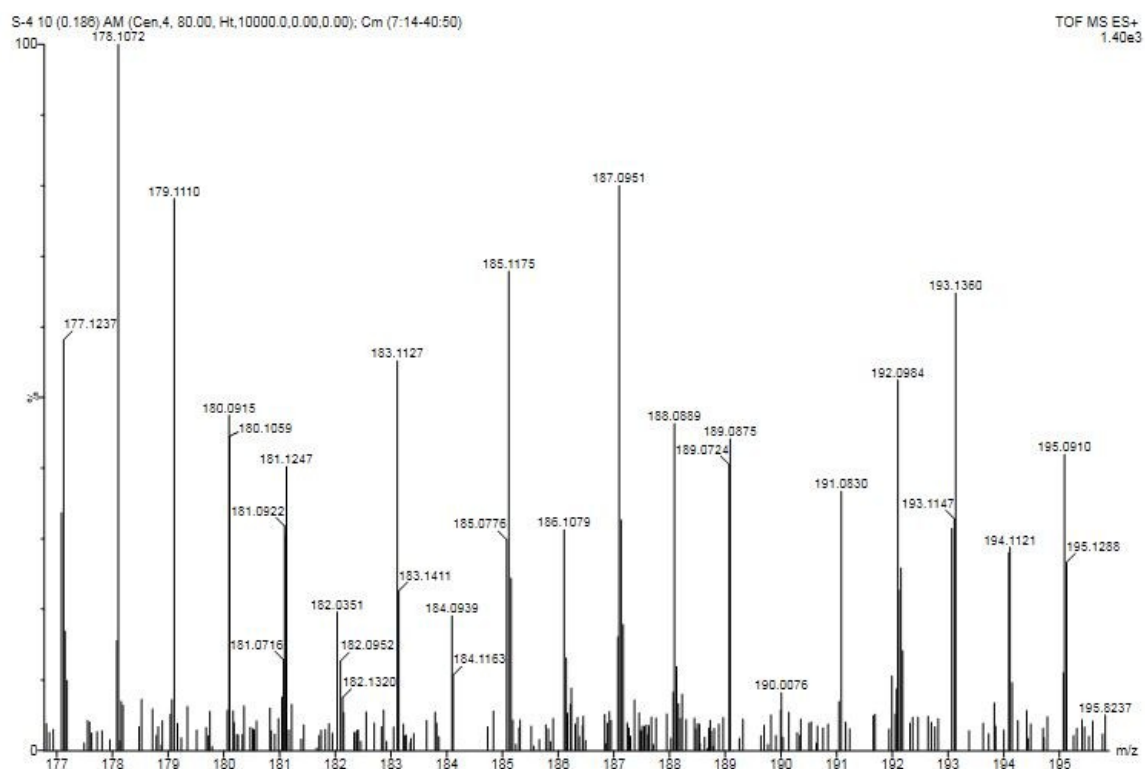
Figure S16. HRMS of 4-hydroxybut-2-yn-1-yl hexanoate.

Figure S17. 1HNMR spectrum of 4-hydroxybut-2-yn-1-yl heptanoate.
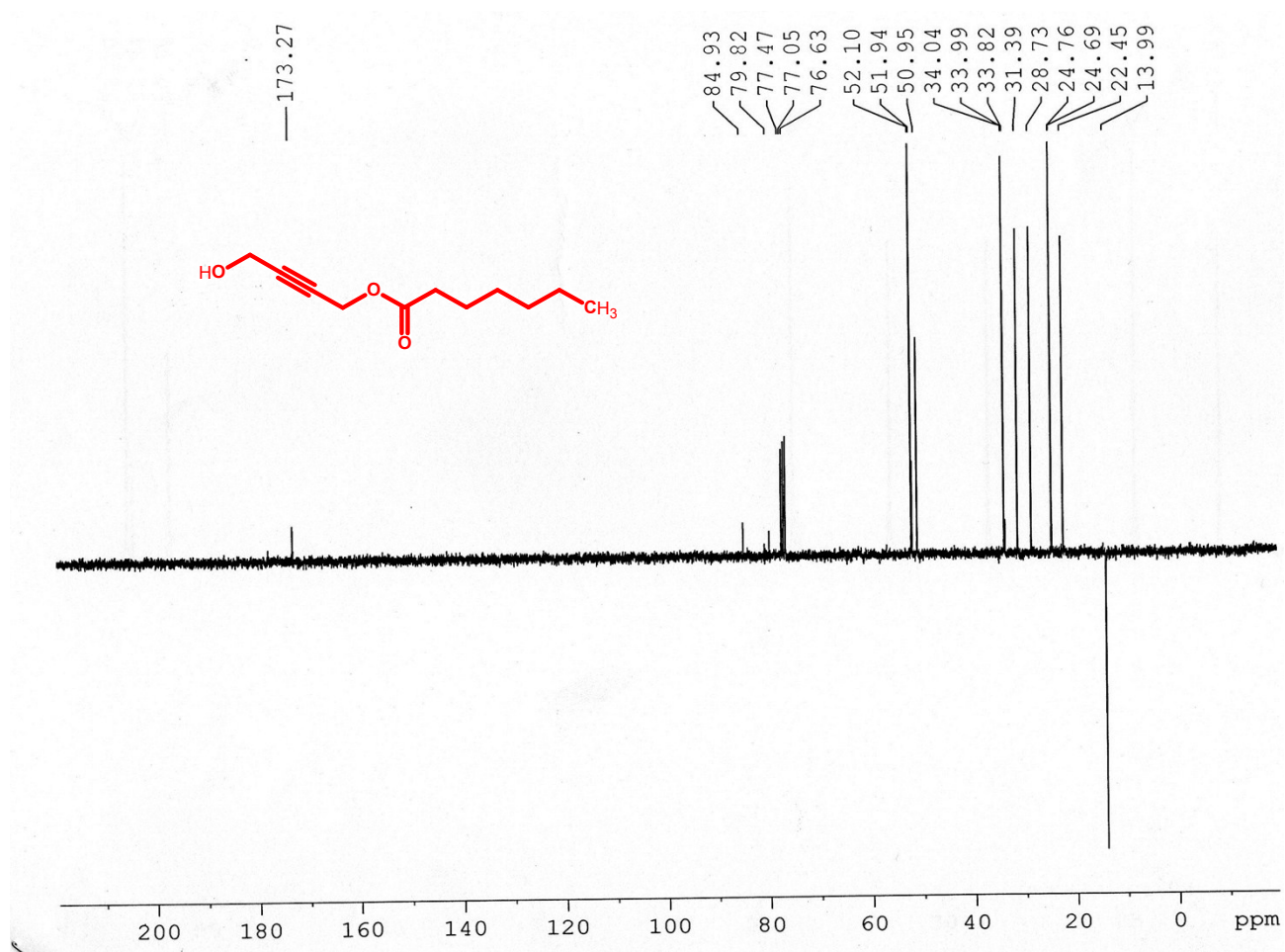
Figure S18. APT of 4-hydroxybut-2-yn-1-yl heptanoate.

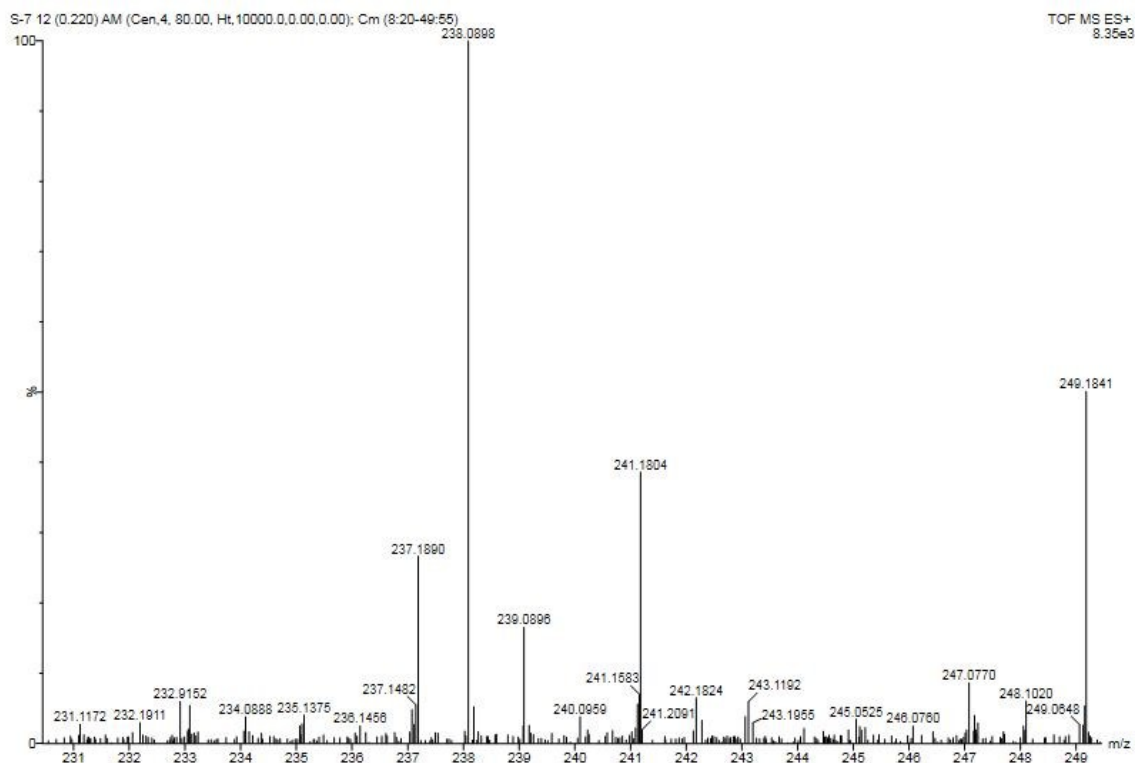**Figure S19. FTIR spectrum of 4-hydroxybut-2-yn-1-yl heptanoate.**

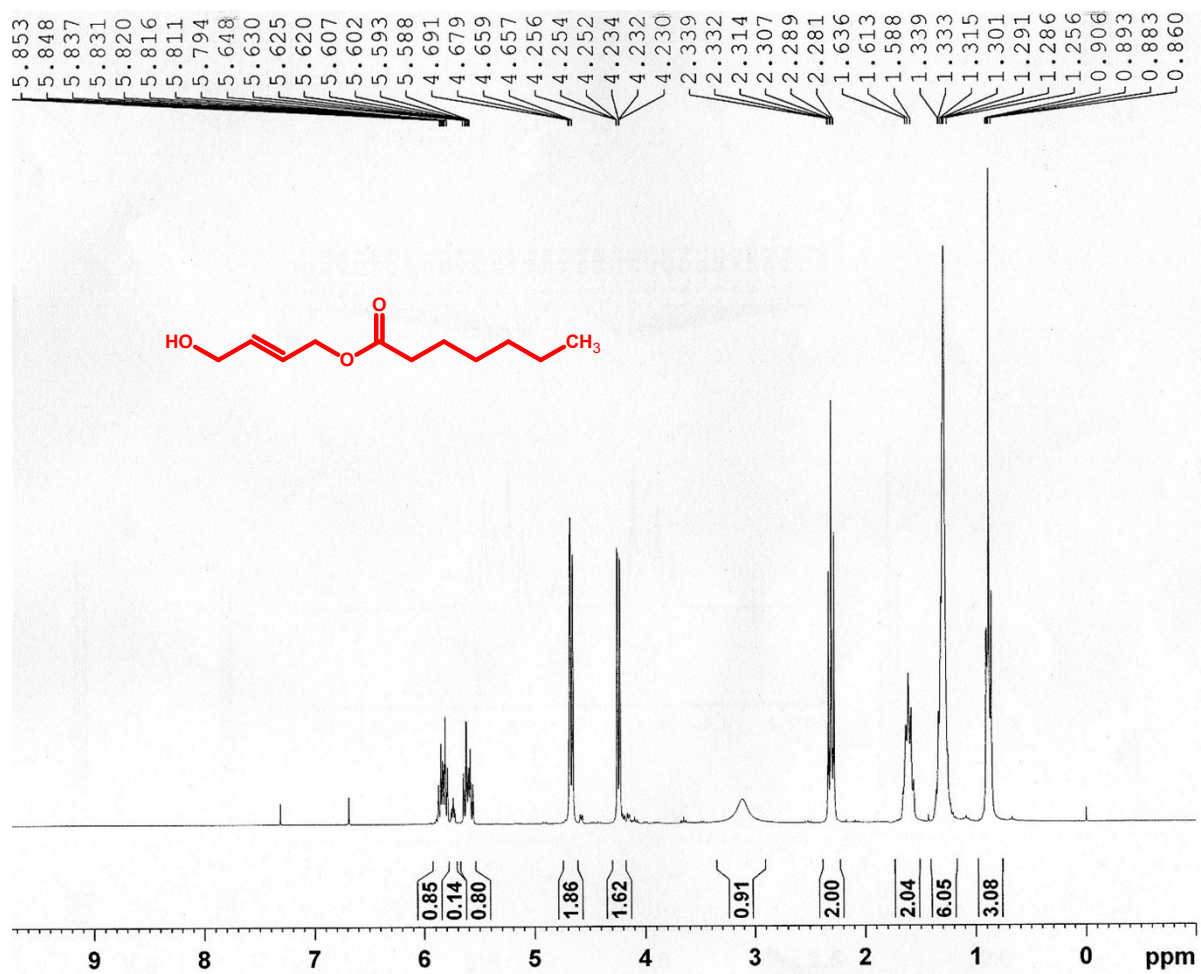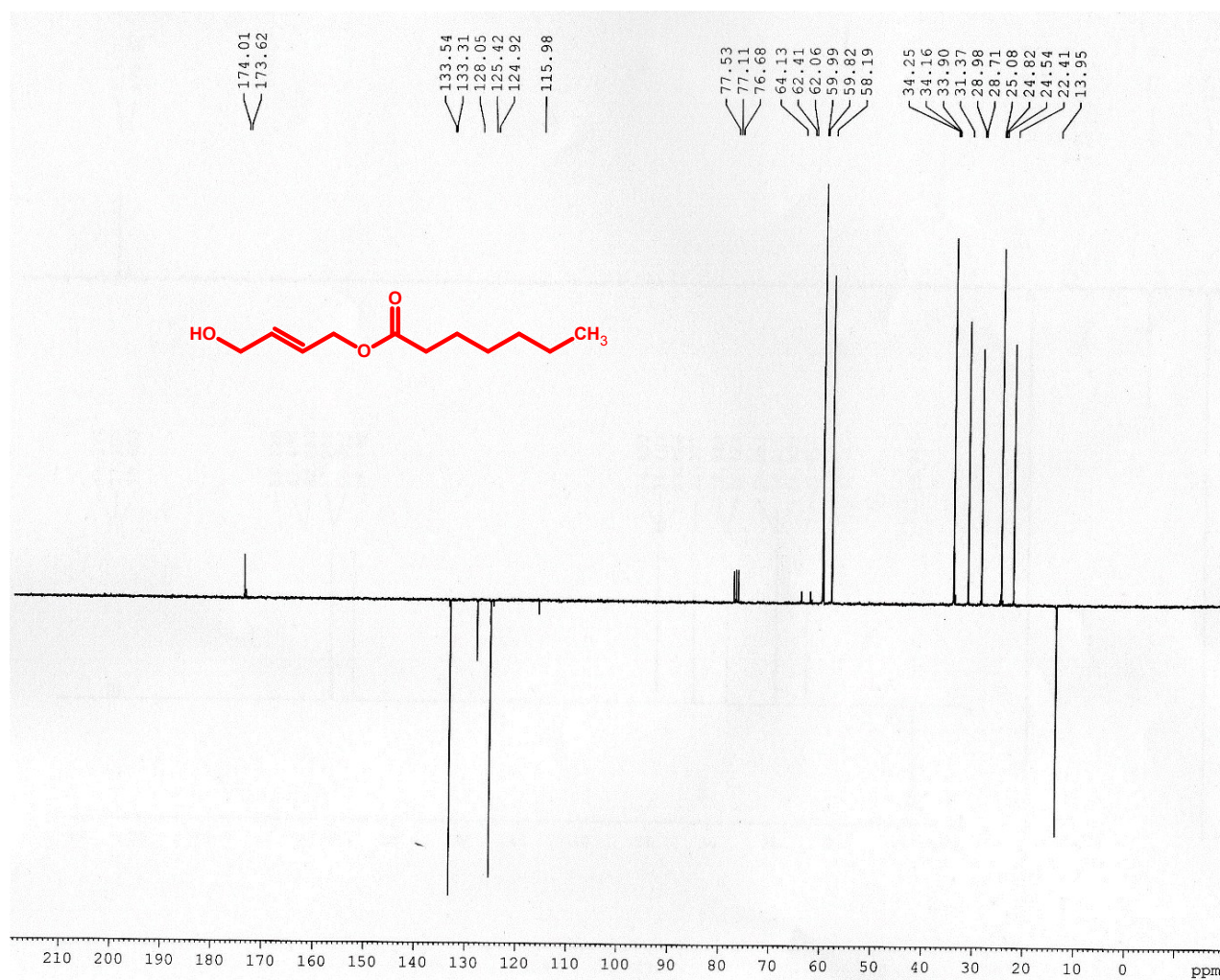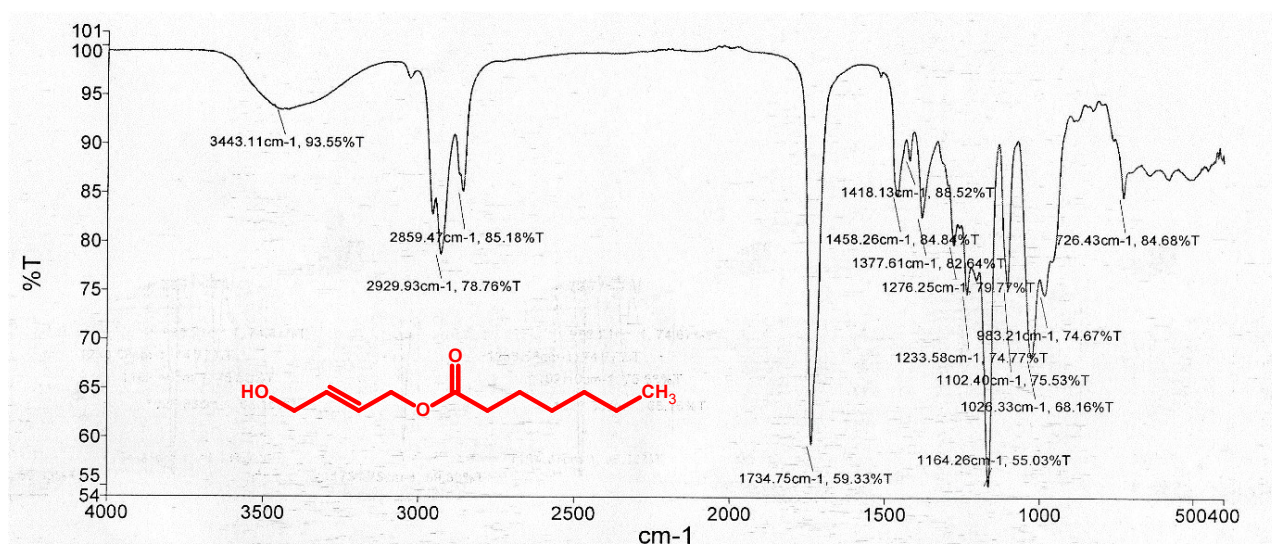**Figure S20. HRMS of 4-hydroxybut-2-yn-1-yl heptanoate.**

7.284
6.014
4.712
4.706
4.309
4.303
4.297
2.369
2.365
2.341
2.318
2.315
1.654
1.631
1.607
1.584
1.303
1.283
1.229
0.900
0.879
0.856

0.76
1.00
0.90
1.94
2.04
8.09
3.03

Figure S21. 1HNMR spectrum of 4-hydroxybut-2-yn-1-yl octanoate.

Figure S22. APT of 4-hydroxybut-2-yn-1-yl octanoate.

Figure S23. FTIR spectrum of 4-hydroxybut-2-yn-1-yl octanoate.

Figure S24. HRMS of 4-hydroxybut-2-yn-1-yl octanoate.

Figure S25. 1HNMR spectrum of 4-hydroxybut-2-yn-1-yl decanoate.

Figure S26. APT of 4-hydroxybut-2-yn-1-yl decanoate.

Figure S27. FTIR spectrum of 4-hydroxybut-2-yn-1-yl decanoate.

Figure S28. HRMS of 4-hydroxybut-2-yn-1-yl decanoate.

Figure S29. 1HNMR spectrum of (2*E*)-4-hydroxybut-2-en-1-yl heptanoate.

Figure S30. APT of (2*E*)-4-hydroxybut-2-en-1-yl heptanoate.

Figure S31. FTIR spectrum of (2*E*)-4-hydroxybut-2-en-1-yl heptanoate.
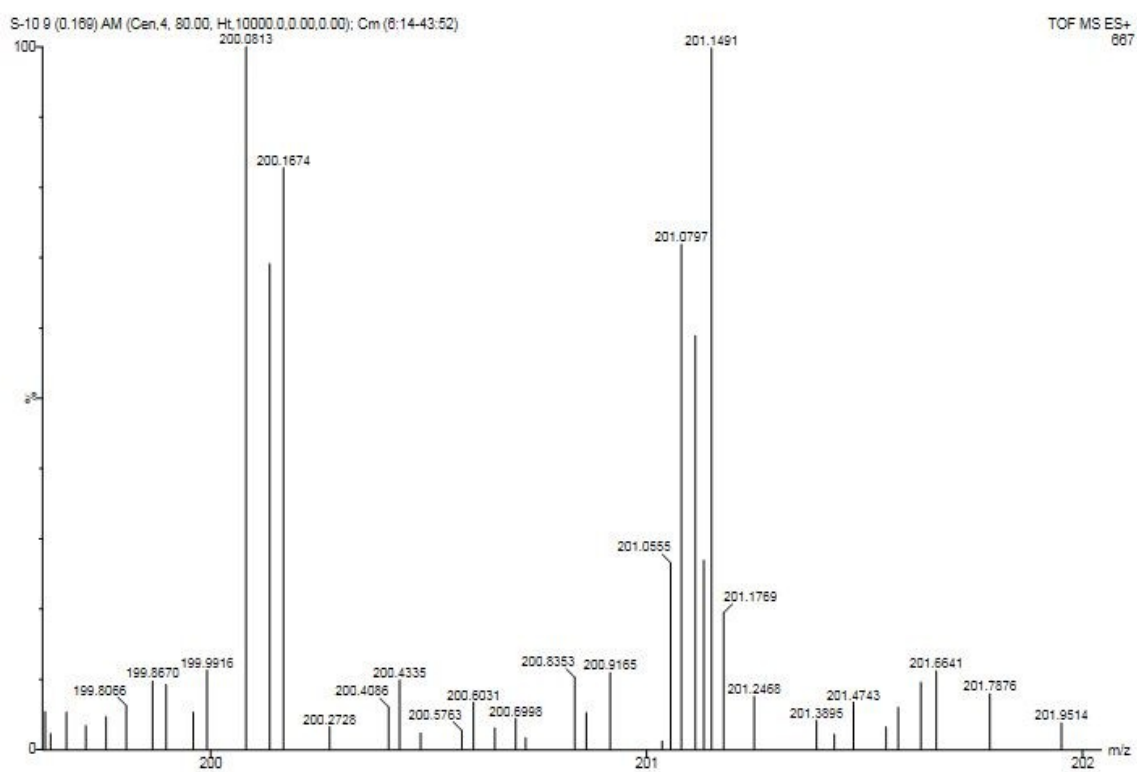
Figure S32. HRMS of (2*E*)-4-hydroxybut-2-en-1-yl heptanoate.
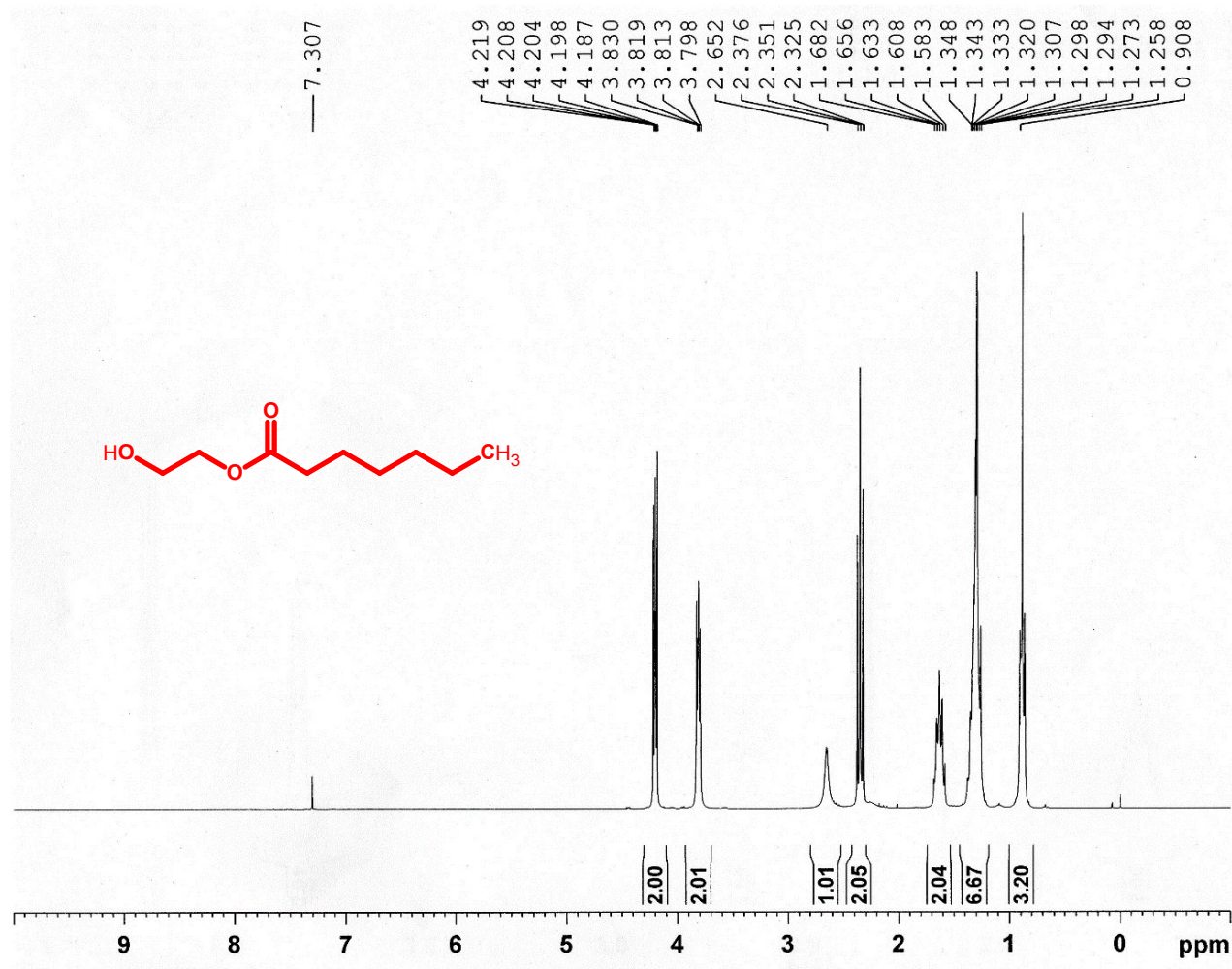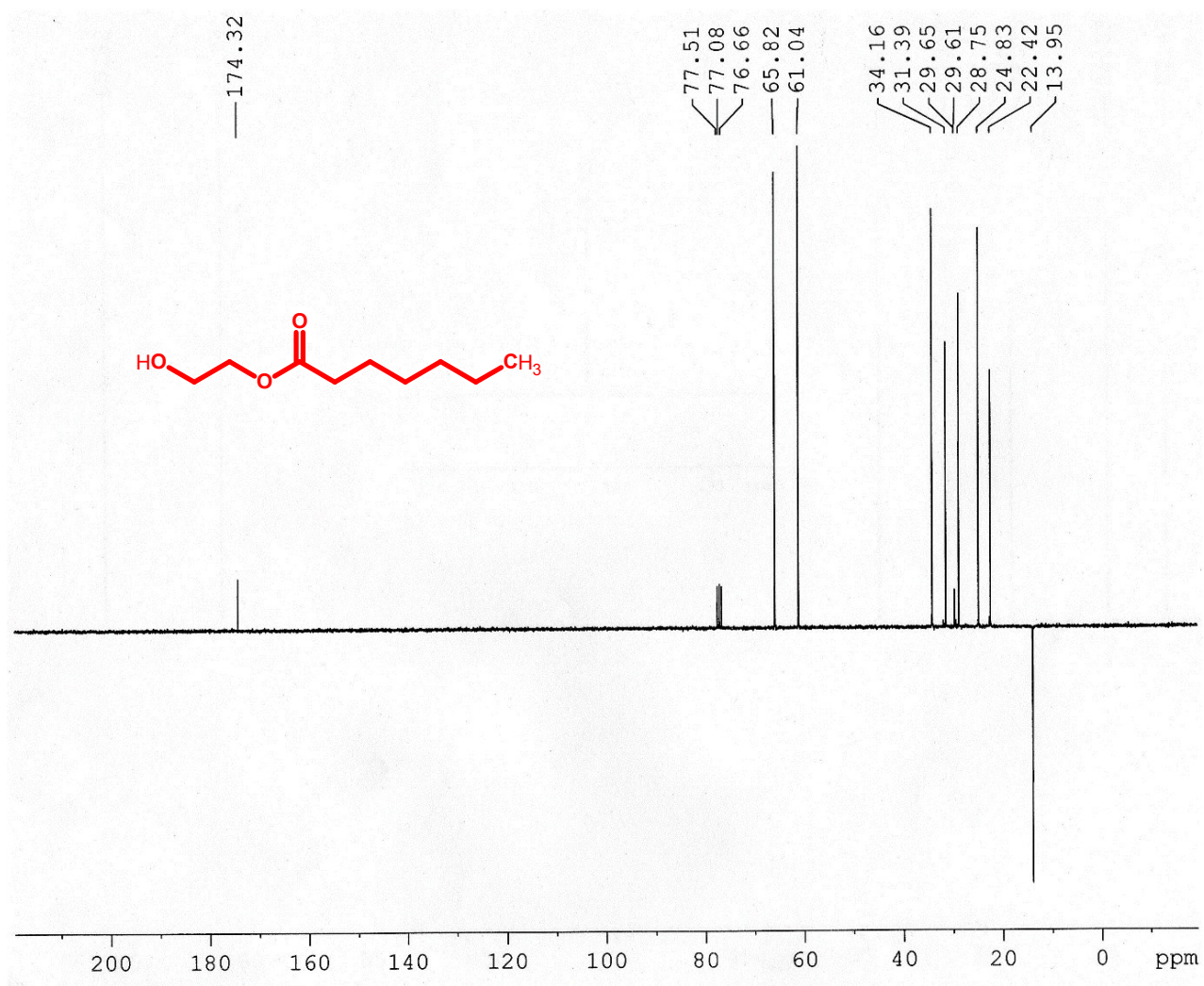
Figure S33. 1HNMR spectrum of 2-hydroxyethyl heptanoate.
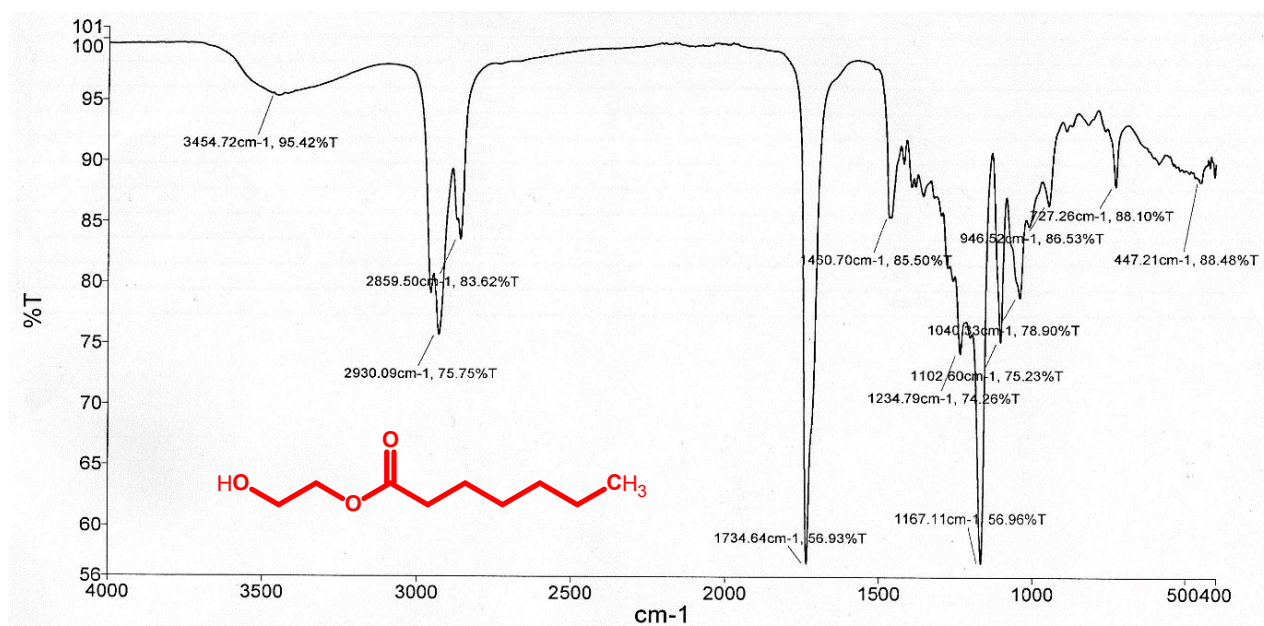
Figure S34. APT of 2-hydroxyethyl heptanoate.
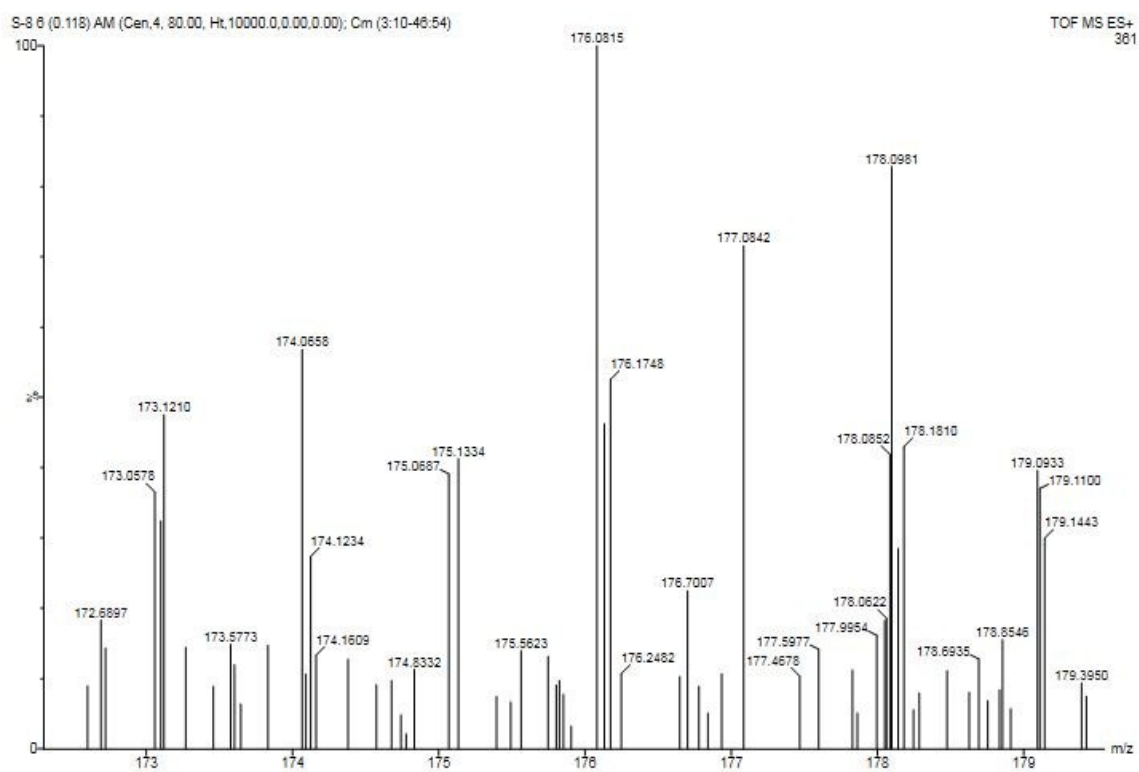
Figure S35. FTIR spectrum of 2-hydroxyethyl heptanoate.

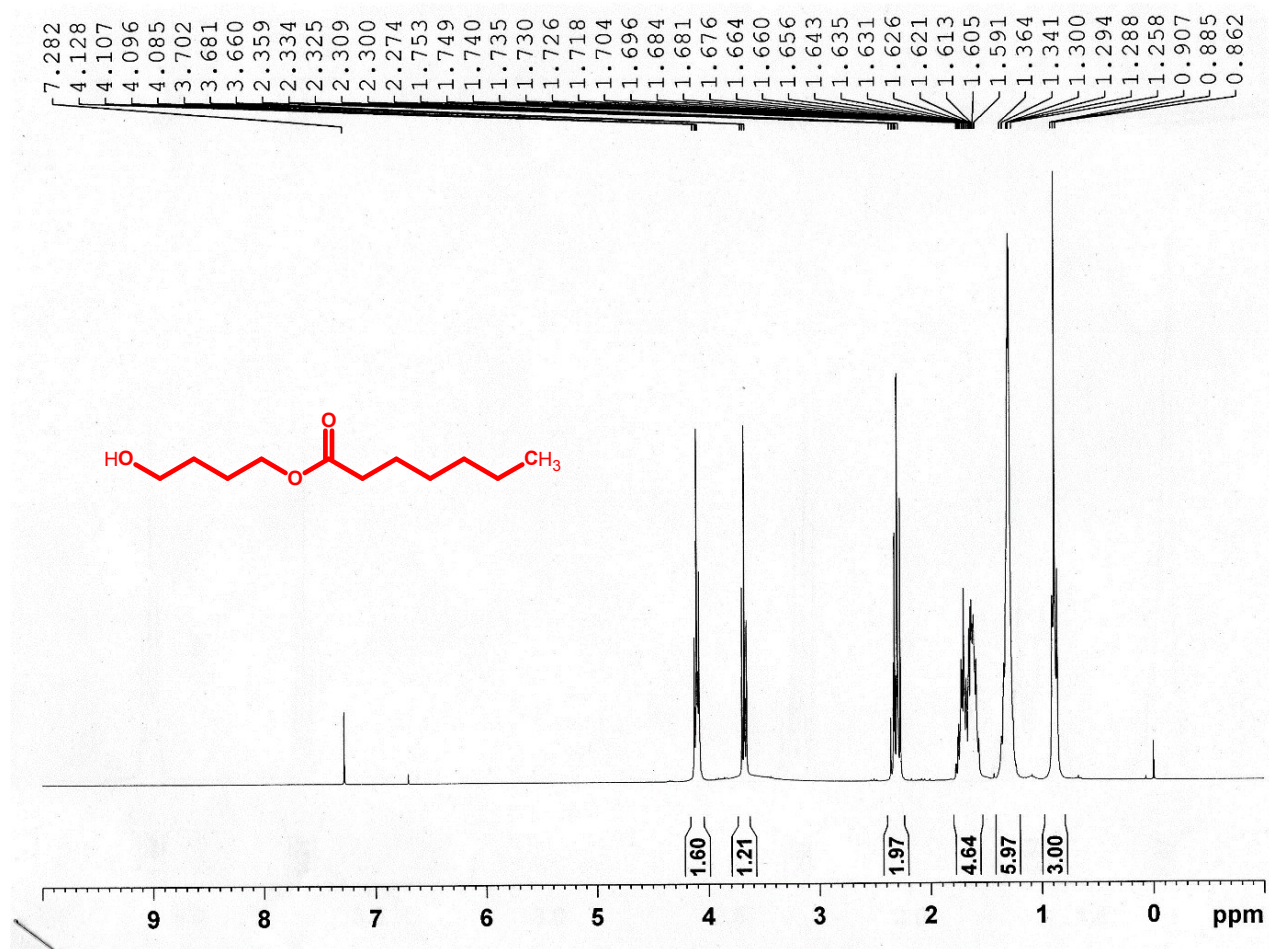**Figure S36. HRMS of 2-hydroxyethyl heptanoate.**

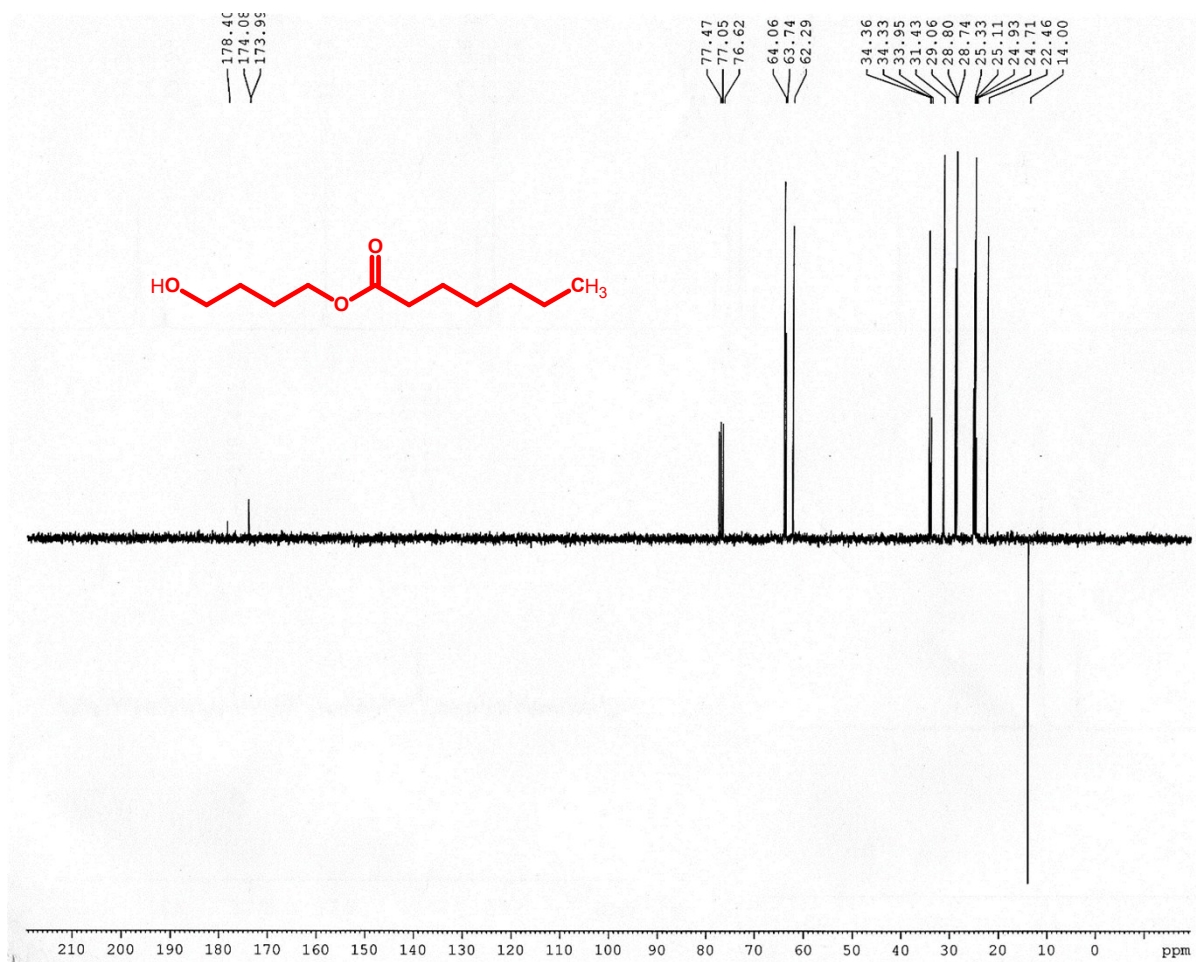**Figure S37. 1HNMR spectrum of 4-hydroxybutyl heptanoate.**

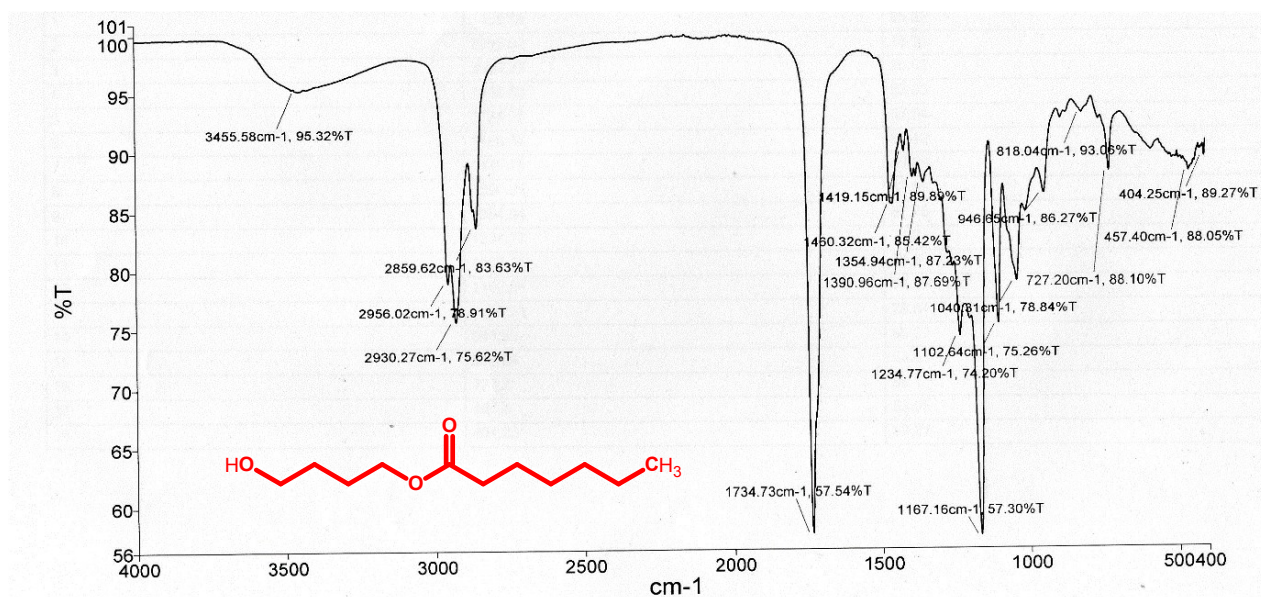**Figure S38. APT of 4-hydroxybutyl heptanoate.**

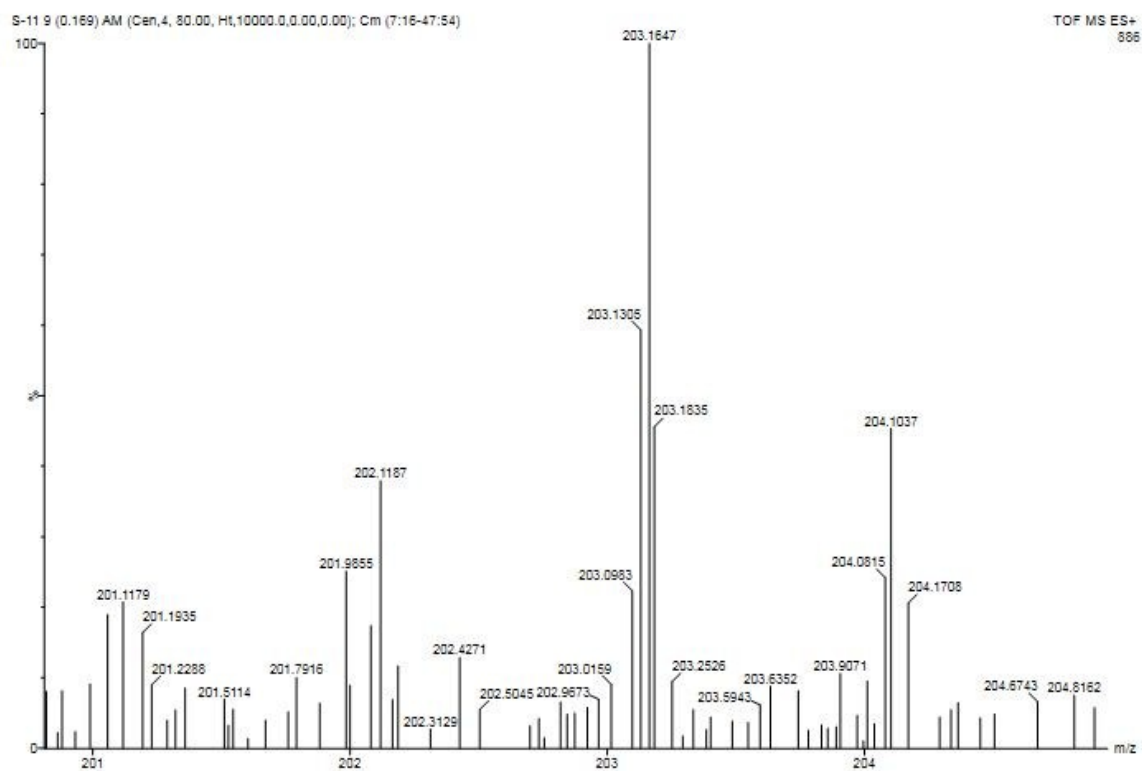**Figure S39: FTIR spectrum of 4-hydroxybutyl heptanoate.**
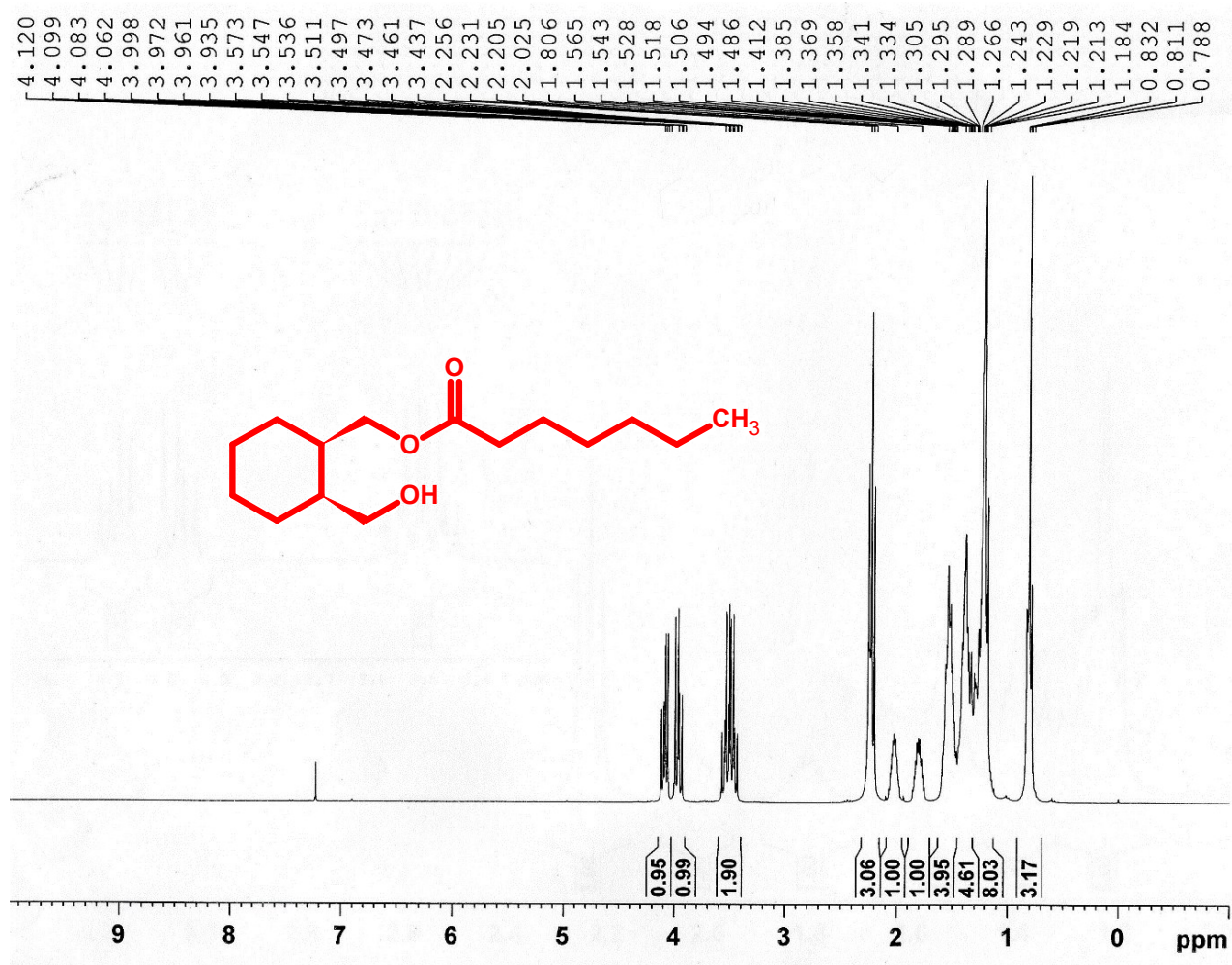

Figure S40: HRMS of 4-hydroxybutyl heptanoate.

Figure S41: 1HNMR spectrum of [2-(hydroxymethyl)cyclohexyl]methyl heptanoate.

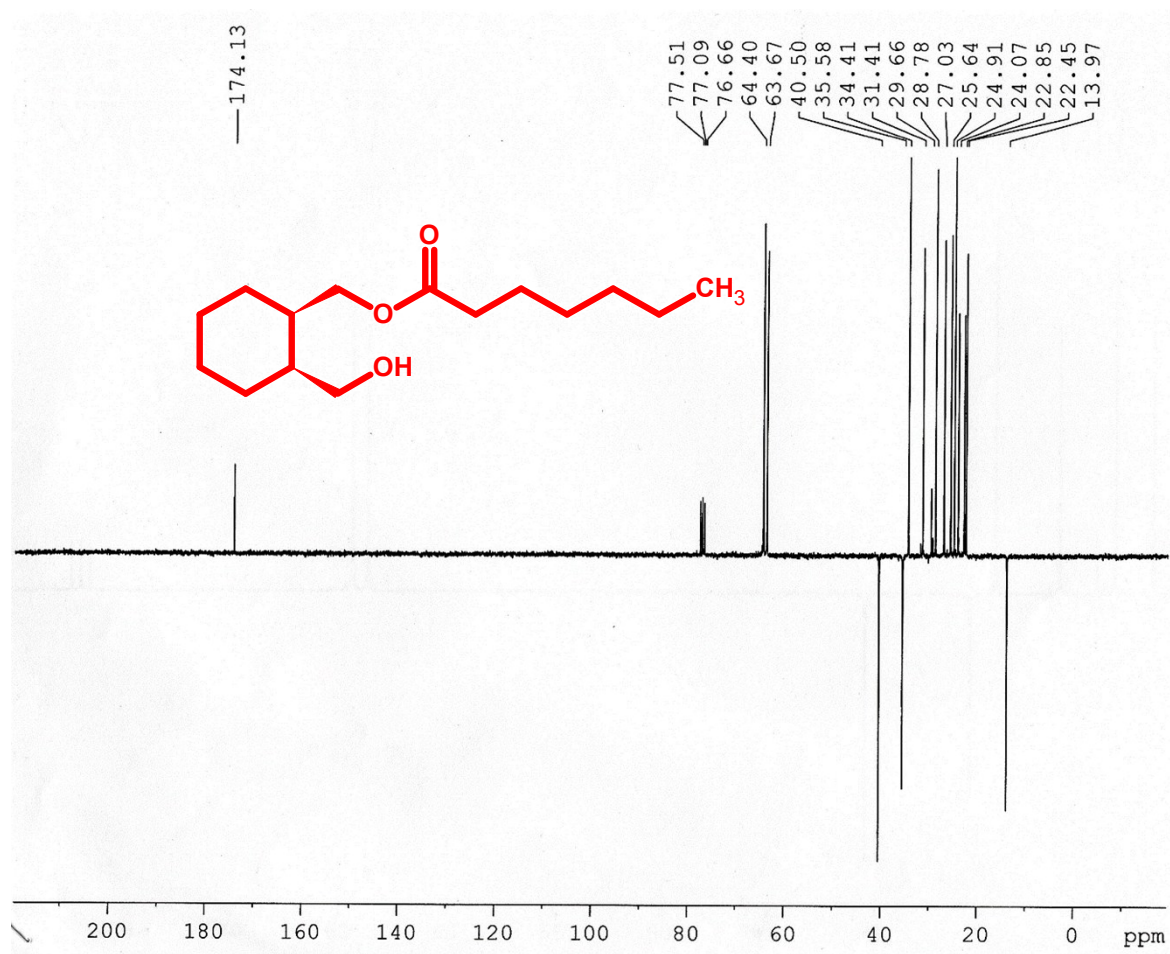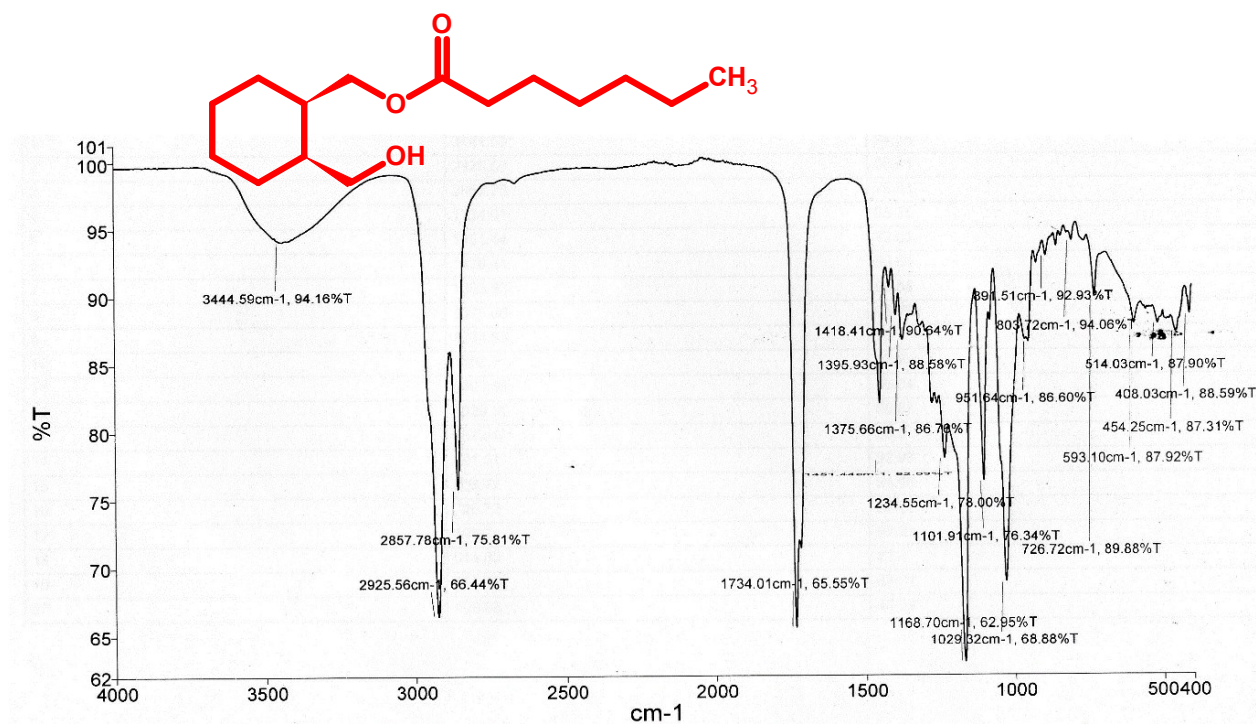**Figure S42: APT of [2-(hydroxymethyl)cyclohexyl]methyl heptanoate.**

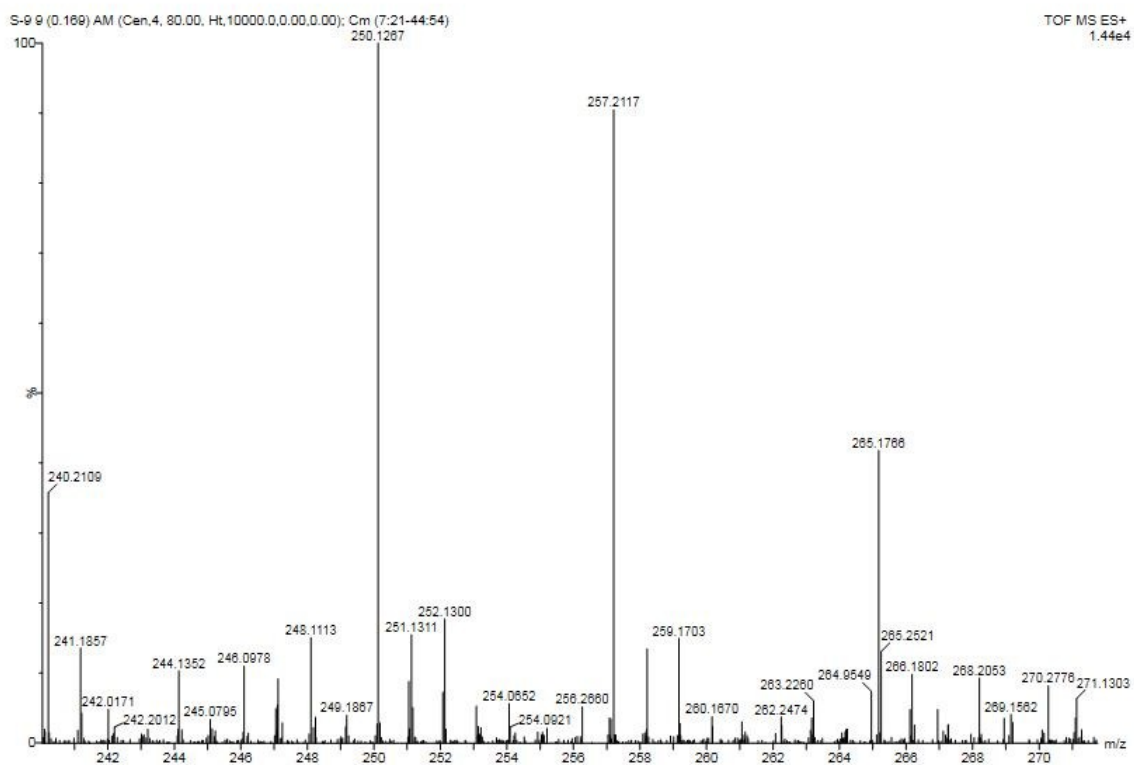**Figure S43: FTIR spectrum of [2-(hydroxymethyl)cyclohexyl]methyl heptanoate.**

Figure S44: HRMS of [2-(hydroxymethyl)cyclohexyl]methyl heptanoate.

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19. C. Yu, B. Liu and L. Hu, *Tetrahedron Lett.*, 2000, **41**, 4281-4285.

20. A. S. Nagle, R. N. Salvatore, R. M. Cross, E. A. Kapxhiu, S. Sahab, C. H. Yoon and K. W. Jung, *Tetrahedron Lett.,* 2003, **44**, 5695–5698.

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