Electronic Supplementary Information

An E-factor minimized protocol for the preparation of methyl β-hydroxy esters

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CONTENTS

Experimental Section

All chemicals were purchased and used without any further purification. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz, 100.6 MHz respectively, using a convenient deuterated solvent (reported in the characterization charts) and the residual peak as internal standard, or TMS in the case of $CDCl_3$. IR spectra were recorded with FT-IR instrument, using $CHCl_3$ as solvent. Column chromatographies were performed by using silica gel 230-400 mesh and eluting as reported in the following characterization charts. Amberlite IRA900F (Amb-F) was purchased from Aldrich as “Fluoride on polymer support”.

Compounds **3b**[1], **3g**[2], **3h**[1], **3i**[1], **3k**[3], and **3l**[4] are known compounds, products **3a, 3c, 3d, 3e, 3f, 3g, 3j** and **6h** are new compounds.

Characterization data and copies of the ^1H and ^{13}C NMR spectra for compounds **3a-l** and **6h** are reported below.

References

(1) Fujisawa, H.; Nakagawa, T.; Mukaiyama, T. *Adv. Synth. Catal*. **2004**, *346*, 1241.
(2) Takeuchi, M.; Akiyama, M.; Kobayashi, S. *J. Am. Chem. Soc*. **2005**, *127*, 13096.
(3) Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Org. Biomol. Chem*. **2004**, *2*, 3401.
(4) Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron*, **2000**, *56*, 7309.

E-factor calculation (Waste produced (g)/ Product (g)), fort he preparation of β-hydroxy ester 3b by a the Mukaiyama aldol reaction of 1 mmol of benzaldehyde (1b) with methyl trimethylsilyl dimethylketene acetal (2), and consequent desilylation step.
Not including the catalyst, silica-gel column chromatography, brine and drying agents.

E-factor= waste (g)/product (g)

Calculation of E-factor has been performed understanding that not in all the cases reported in the literatures, Authors have been paid attention to the waste minimization in the setting of their protocols.

When the Authors have not reported the amount of solvent used in the work-up procedure, we have accounted fort he same amount we used (2 x 2 mL of Et_2O)

- J. J. Song, Z. Tan, J. T. Reeves, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2007**, *9,* 1013-1016.

E-factor = [0.106 g (benzaldehyde) + 4.45 g (THF) + 0.220 g (methyl trimethylsilyl dimethylketene acetal) + 2.36 g (aqueous HCl) + 44 g (CH_2Cl_2) – 0.158 g (product x yield)] / 0.158 g = **322.65**
Not accounting for column chromatography

- T. Mukaiyama, H. Fujisawa, T. Nakagawa, *Helv. Chim. Acta* **2002**, *85*, 4518-4531.

E-factor = [1.18 g (DMF) + 0.255 g (methyl trimethylsilyl dimethylketene acetal) + 0.59 g (DMF) + 0.106 g (benzaldehyde) + 0.708 g (DMF) + 2.8 g (Et_2O extraction 2 x 2 mL) + 1.28 g (aqueous HCl) + 3.33 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.200 g (product x yield)] / 0.200 g = **64.24**
Not accounting for column chromatography

- Z. -L. Schen, S. -J. Ji, T. -P. Loh, *Tetrahedron Lett.* **2005**, *46*, 507-508.

E-factor = [0.106 g (benzaldehyde) + 0.364 g (methyl trimethylsilyl dimethylketene acetal) 1.78 g (THF) + 2.72 g (aqueous HCl) + 21.18 g (Et_2O extraction 3 x 10 mL) – 0.160 g (product x yield)] / 0.160 = **162.44**
Not accounting for column chromatography

- S. -L. Chen, S. -J. Ji, T. -P. Loh, *Tetrahedron Lett.* **2004**, *45*, 375-377.

E-factor = [0.106 g (benzaldehyde) + 0.200 g + 0.200 g (methyl trimethylsilyl dimethylketene acetal) 0.552 g ([omim]Cl)* + 2.72 g (aqueous HCl) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.150 g (product x yield)] / 0.150 = **42.85**
Not accounting for column chromatography
*Density value 1.10395 taken from Romanì et al Fluid Phase Equilibria **2007**, *252*, 96–102.

- A. Heydaria, S. Khaksara, M. Sheykhana, M. Tajbakhshb *J. Mol. Catal. A:* **2008**, *287,* 5-8.

E-factor = [0.106 g (benzaldehyde) + 1.57 g (MeCN) + 0.182 g (methyl trimethylsilyl dimethylketene acetal) + 3.31 g + 3.31 g (CH_2Cl_2) – 0.177 g (product x yield)] / 0.177 g= **46.91**
Not accounting for column chromatography

- Our batch conditions:

E-factor = [0.106 g (benzaldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.166 g (product x yield)] / 0.166 g = **28.87**

E-factor for all the substrates ranges from 19.6 - 28.9 see below for details in each case.

- **Our cyclic continuous flow conditions:**

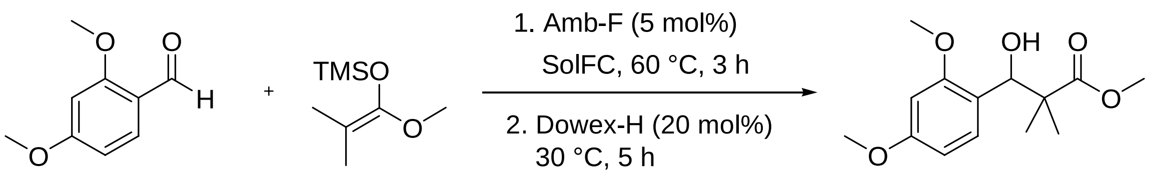
E-factor = [0.106 g (benzaldehyde) + 0.223 g (methyl trimethylsilyl dimethylketene acetal) + 0.178 g (THF) – 0.177 g (product x yield)] / 0.177 g = **1.86**

E-factor for the three substrates ranges from 1.41 - 2.09

Beside the solvent used for the work-up procedures, it can certainly be concluded that in our case the most significant contribution to the E-factor minimization is due to the elimination of aqueous HCl waste, thanks to the novel de-silylation process promoted by Dowex 50Wx8 H.

The dramatic reduction of E-factor in the case of our cyclic continuous flow conditions it is certainly the proof that the combination of flow conditions, solvent-free conditions and solid recoverable catalysts, represents an efficient approach form minimizing the environmental cost of organic synthesis
In addition, in terms of labor time an automated process is clearly more convenient than a step-by-step process.

Chem. Name	**Methyl 3-(2',4'-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (3a)**
Lit. Ref.	----



1a **2** **3a**

Mol.Wt.: 268

METHOD:

In a screw capped vial equipped with a magnetic stirrer 2,4-dimethoxybenzaldehyde (**1a**) (0.166 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate, coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure product methyl 3-(2',4'-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**3a**) as a colorless oil (91% yield, 0.244 g).

E-factor = 19.6

[0.166 g (aldehyde) + 0.273g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.244 g (product x yield)] / 0.244 g

Mol Formula	$C_{14}H_{20}O_5$	**m.p.**	Oil

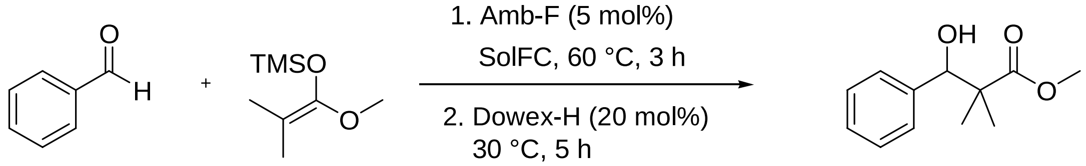
FT-IR ($CHCl_3$, cm^{-1}): 3532, 3011, 1713.

Elemental Analysis: Calcd. C, 62.67; H, 7.51; found C, 62.53; H, 7.68.

	δ value	**No. H**	**Mult.**	**j value/Hz**
^{1}H NMR 400 MHz $CDCl_3$	1.10	3	*s*	
	1.14	3	*s*	
	3.42	1	*d*	6.3
	3.71	3	*s*	
	3.78	3	*s*	
	3.80	3	*s*	
	5.20	1	*d*	6.2
	6.43	1	*d*	1.9
	6.46	1	*dd*	8.8, 2.0
	7.20	1	*d*	8.4

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 18.9, 22.8, 48.5, 51.8, 55.0, 55.1, 73.4, 98.1, 104.0, 120.5, 129.5, 157.9, 160.0, 178.1.

Chem. Name	**Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (3b)**
Lit. Ref.	*Adv. Synth. Catal.* **2004**, *346*, 1241.



1b **2** **3b**

Mol.Wt.: 208

METHOD:
In a screw capped vial equipped with a magnetic stirrer benzaldehyde (**1b**) (0.106 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate, coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (**3b**) as a white solid (80% yield, 0.166 g) which was re-crystallized from *n*-Hexane/ EtOAc 9/1.
E-factor = 28.9
[0.106 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.166 g (product x yield)] / 0.166 g

Mol Formula	$C_{12}H_{16}O_3$	**m.p.**	68-69 °C (*n*-Hexane/ EtOAc 9/1)

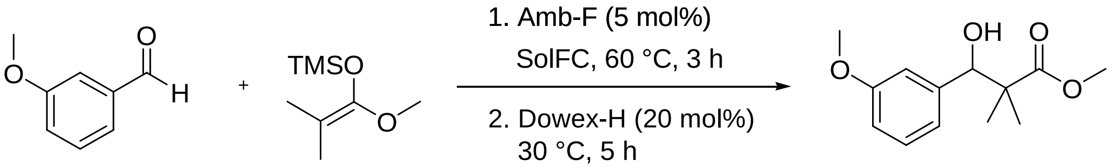
FT-IR ($CHCl_3$, cm^{-1}): 3604, 3015, 1715.

Elemental Analysis: Calcd. C, 69.21; H, 7.74; found C, 69.02; H, 7.50.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**	
	1.11	3	*s*		
	1.15	3	*s*		
	3.07	1	*d*	4.2	
	3.72	3	*s*		
	4.90	1	*d*	4.1	
	7.31	5	*m*		

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 18.9, 22.9, 47.6, 52.0, 78.6, 127.5, 127.7 (one aromatic carbon is missing), 139.9, 178.0.

Chem. Name	**Methyl 3-hydroxy-3-(3'-methoxyphenyl)-2,2-dimethylpropanoate (3c)**
Lit. Ref.	---



1c **2** **3c**

Mol.Wt.: 238

METHOD:
In a screw capped vial equipped with a magnetic stirrer 3-methoxybenzaldehyde (**1c**) (0.136 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**), (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure methyl 3-hydroxy-3-(3'-methoxyphenyl)-2,2-dimethylpropanoate (**3c**) as a colorless oil (87% yield, 0.207 g).
E-factor = 23.1
[0.136 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.207 g (product x yield)] / 0.207 g

Mol Formula	$C_{13}H_{18}O_4$	**m.p.**	Oil

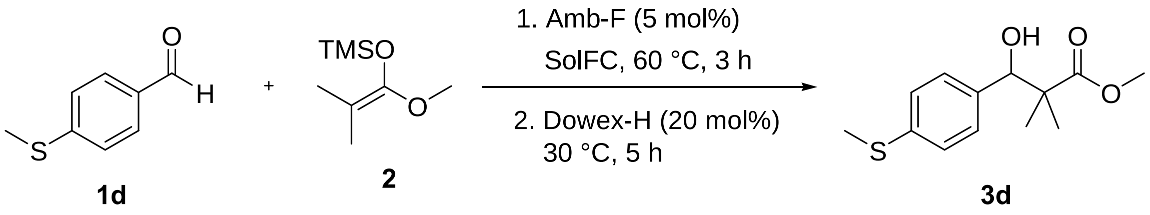
FT-IR ($CHCl_3$, cm^{-1}): 3602, 2876, 1719.

Elemental Analysis: Calcd. C, 65.53; H, 7.61; found C, 65.70; H, 7.42.

	δ value	**No. H**	**Mult.**	**j value/Hz**
^1H NMR 400 MHz $CDCl_3$	1.10	3	*s*	
	1.14	3	*s*	
	3.13	1	*d*	4.2
	3.70	3	*s*	
	3.78	3	*s*	
	4.85	1	*d*	4.1
	6.81	1	*d*	8.2
	6.85	2	*m*	
	7.21	1	*t*	8.1

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 19.1, 22.9, 47.6, 52.0, 55.1, 78.5, 113.0, 113.3, 120.0, 128.6, 141.6, 159.0, 178.0.

Chem. Name	**Methyl 3-hydroxy-2,2-dimethyl-3-[4’-(methylthio)phenyl]propanoate (3d)**
Lit. Ref.	---



Mol.Wt.: 254

METHOD:

In a screw capped vial equipped with a magnetic stirrer 4-methylthiobenzaldehyde (**1d**) (0.152 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure methyl methyl 3-hydroxy-2,2-dimethyl-3-[4’-(methylthio)phenyl]propanoate (**3d**) as a white solid (85% yield, 0.216 g) which was re-crystallized from *n*-Hexane/ EtOAc 9/1.

E-factor = 22.2

[0.152 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.216 g (product x yield)] / 0.216 g

Mol Formula	$C_{13}H_{18}O_3S$	**m.p.**	66-67 °C (*n*-Hexane/ EtOAc 9/1)

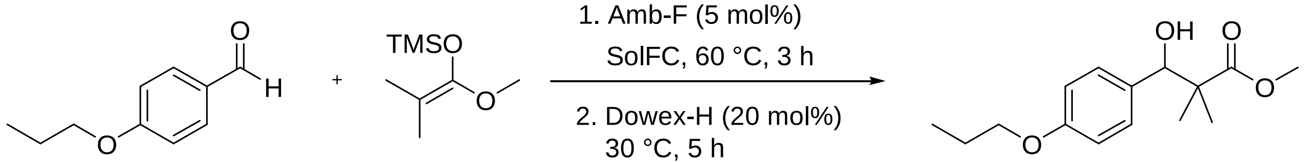
FT-IR ($CHCl_3$, cm^{-1}): 3609, 2999, 1717.

Elemental Analysis: Calcd. C, 61.39; H, 7.13; S, 12.61; found C; 61.09 H, 7.21 ; S, 12.17.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**
	1.09	3	*s*	
	1.12	3	*s*	
	2.47	3	*s*	
	3.09	1	*d*	4.0
	3.71	3	*s*	
	4.84	1	*d*	4.1
	7.20	4	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 15.6, 18.9, 22.9, 47.6, 52.0, 78.2, 125.7, 128.0, 136.7, 137.7, 178.0.

Chem. Name	**Methyl 3-hydroxy-2,2-dimethyl-3-(4’-propoxyphenyl)propanoate (3e)**
Lit. Ref.	---



1e **2** **3e**

Mol.Wt.: 266

METHOD:
In a screw capped vial equipped with a magnetic stirrer 4-propoxybenzaldehyde (**1e**) (0.164 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure methyl 3-hydroxy-2,2-dimethyl-3-(4’-propoxyphenyl)propanoate (**3e**) as a colorless oil (83% yield, 0.221 g).
E-factor = 21.7
[0.164 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.221 g (product x yield)] / 0.221 g

Mol Formula	$C_{15}H_{22}O_4$	**m.p.**	Oil

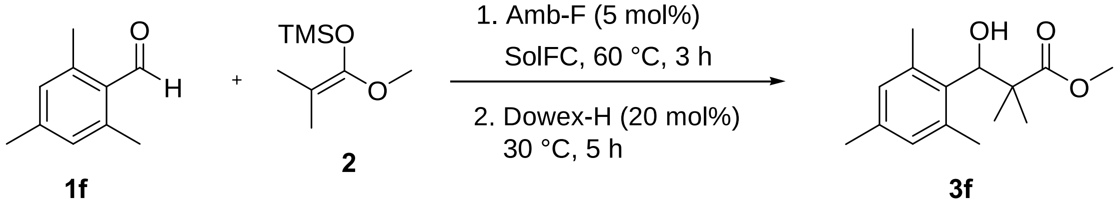
FT-IR ($CHCl_3$, cm^{-1}): 3592, 2966, 1713.

Elemental Analysis: Calcd. C, 67.64; H, 8.33; found C, 67.39 H, 8.16.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**
	1.03	3	*t*	7.4
	1.08	3	*s*	
	1.13	3	*s*	
	1.80	2	*sex*	21.7, 14.7, 7.5
	3.01	1	*bs*	
	3.70	3	*s*	
	3.90	2	*t*	6.6
	4.83	1	*s*	
	6.83	2	*d*	8.5
	7.19	2	*d*	8.5

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 10.4, 18.9, 22.5, 22.8, 47.7, 51.9, 69.4, 78.2, 116.6, 128.5, 131.8, 158.6, 178.1.

Chem. Name	**Methyl 3-hydroxy-3-mesityl-2,2-dimethylpropanoate (3f)**
Lit. Ref.	---



1f + **2** → **3f**

Mol.Wt.: 250

METHOD:
In a screw capped vial equipped with a magnetic stirrer 2,4,6-trimethylbenzaldehyde (**1f**) (0.148 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure methyl 3-hydroxy-3-mesityl-2,2-dimethylpropanoate (**3f**) as a white solid (89% yield, 0.222 g) which was re-crystallized from *n*-Hexane/ EtOAc 9/1.
E-factor = 21.5
[0.148 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.222 g (product x yield)] / 0.222 g

Mol Formula	$C_{15}H_{22}O_3$	**m.p.**	64-65 °C (*n*-Hexane/ EtOAc 9/1)

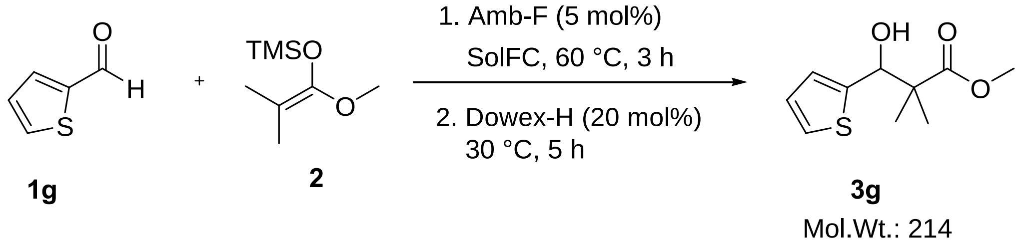
FT-IR ($CHCl_3$, cm^{-1}): 3610, 2954, 1717.

Elemental Analysis: Calcd. C, 71.97; H, 8.86; found C, 72.13; H, 8.64.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**
	1.14	3	*s*	
	1.26	3	*s*	
	2.25	3	*s*	
	2.35	3	*s*	
	2.40	3	*s*	
	2.81	1	*d*	3.8
	3.75	3	*s*	
	5.57	1	*d*	3.5
	6.82	1	*bs*	
	6.84	1	*bs*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 20.5, 20.6, 22.1, 23.9, 49.9, 52.0, 75.7, 76.6, 76.9, 77.3, 129.1, 131.7, 132.2, 136.4, 178.5.

Chem. Name	**Methyl 3-hydroxy-2,2-dimethyl-3-thien-2’-ylpropanoate (3g)**
Lit. Ref.	-



METHOD:

In a screw capped vial equipped with a magnetic stirrer thiophene-2-carbaldehyde (**1g**) (0.112 g, 1.0mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure methyl 3-hydroxy-2,2-dimethyl-3-thien-2’-ylpropanoate (**3g**) as a white solid (82% yield, 0.175 g) which was re-crystallized from *n*-Hexane/ EtOAc 9/1.

E-factor = 27.4

[0.112 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.175 g (product x yield)] / 0.175 g

Mol Formula	$C_{10}H_{14}O_3S$	**m.p.**	52-53 °C (*n*-Hexane/ EtOAc 9/1)

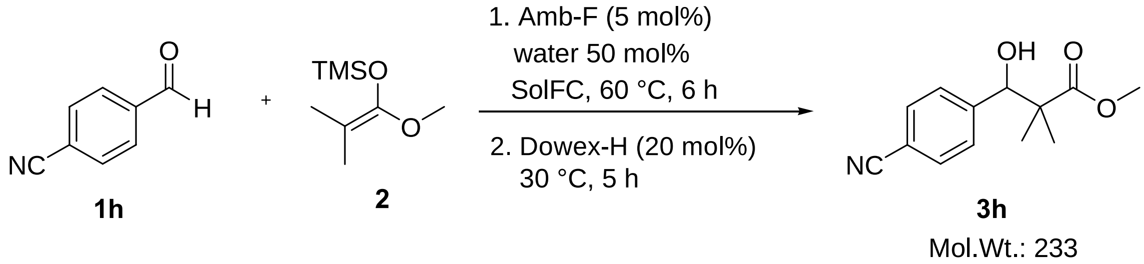
FT-IR ($CHCl_3$, cm^{-1}): 3599, 3010, 1712.

Elemental Analysis: Calcd. C, 56.05; H, 6.59; S, 14.96; found C, 5623; H, 6.38; S, 14.81.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**
	1.20	3	*s*	
	1.22	3	*s*	
	3.33	1	*d*	5.1
	3.73	3	*s*	
	5.10	1	*d*	4.9
	6.95	2	*m*	
	7.23	1	*d*	4.9

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 19.8, 22.7, 47.6, 52.1, 75.5, 124.7, 125.5, 126.1, 143.6, 177.8.

Chem. Name	**Methyl 3-(4’-cyanophenyl)-3-hydroxy-2,2-dimethylpropanoate (3h)**
Lit. Ref.	*Adv. Synth. Catal.* **2004**, *346*, 1241.



METHOD:

In a screw capped vial equipped with a magnetic stirrer 4-cyanobenzaldehyde (**1h**) (0.131 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.638 mL, 3.0 mmol), Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) and de-ionized H_2O (0.009 mL, 0.5 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 6 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give methyl 3-(4’-cyanophenyl)-3-hydroxy-2,2-dimethylpropanoate (**3h**) as a white solid in 95% purity (83% yield, 0.193 g) which was re-crystallized from *n*-Hexane/ EtOAc 9/1.

E-factor = 24.9

[0.131 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 0.009 g (H_2O) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.193 g (product x yield)] / 0.193 g

Mol Formula	$C_{13}H_{15}NO_3$	**m.p.**	100-101 °C (*n*-Hexane/ EtOAc 9/1)

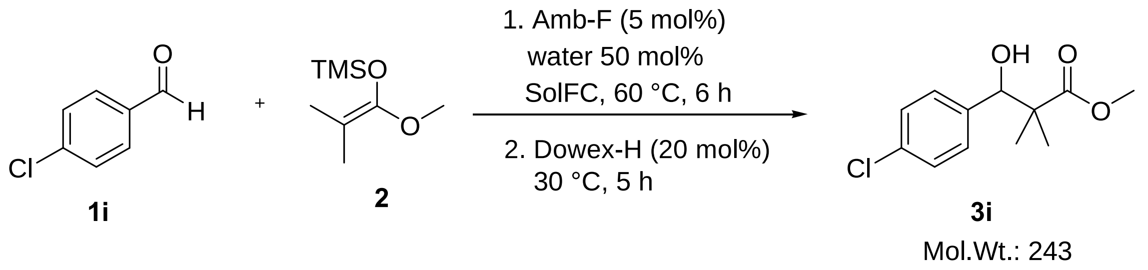
FT-IR ($CHCl_3$, cm^{-1}): 3607, 3011, 2234, 1709.

Elemental Analysis: Calcd. C, 66.94; H, 6.48; N, 6.00; found C, 70.06; H, 6.34; N, 6.17.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**
	1.10	3	*s*	
	1.12	3	*s*	
	3.33	1	*bs*	
	3.72	3	*s*	
	4.94	1	*s*	
	7.42	2	*d*	8.2
	7.61	2	*d*	8.2

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 19.0, 22.6, 47.5, 52.2, 77.8, 111.5, 118.6, 128.3, 131.4, 145.2, 177.6.

Chem. Name	**Methyl 3-(4’-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate (3i)**
Lit. Ref.	*Adv. Synth. Catal.* **2004**, *346*, 1241.



METHOD:
In a screw capped vial equipped with a magnetic stirrer 4-chlorobenzaldehyde (**1i**) (0.140 g, 1.0mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.638 mL, 3.0 mmol), Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) and de-ionized H_2O (0.009 mL, 0.5 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 6 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give methyl 3-(4’-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate (**3i**) as a white solid in 97% purity (85% yield, 0.206 g) which was re-crystallized from *n*-Hexane/ EtOAc 9/1.
E-factor = 23.2
[0.140 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 0.009 g (H_2O) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.207 g (product x yield)] / 0.207 g

Mol Formula	$C_{12}H_{15}ClO_3$	**m.p.**	62-63 °C (*n*-Hexane/ EtOAc 9/1)

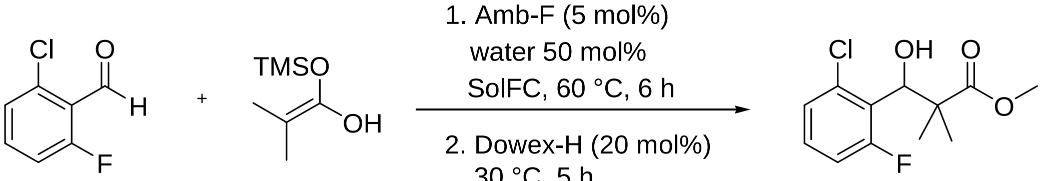
FT-IR ($CHCl_3$, cm^{-1}): 3614, 3008, 1715.

Elemental Analysis: Calcd. C, 59.39; H, 6.23; Cl, 14.61; found C, 59.27; H, 6.16; N, 14.53.

	δ value	**No. H**	**Mult.**	**j value/Hz**
^{1}H NMR 400 MHz $CDCl_3$	1.09	3	*s*	
	1.12	3	*s*	
	3.21	1	*d*	4.2
	3.17	3	*s*	
	4.85	1	*d*	4.2
	7.23	2	*d*	8.5
	7.29	2	*d*	8.5

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 18.9, 22.7, 47.5, 52.1, 77.8, 127.8, 128.9, 133.4, 138.3, 177.9

Chem. Name	**Methyl 3-(2’-chloro-6’-fluorophenyl)-3-hydroxy-2,2-dimethylpropanoate (3j)**
Lit. Ref.	---



1j **2** **3j**

Mol.Wt.: 260

METHOD:
In a screw capped vial equipped with a magnetic stirrer 2-chloro-6-fluorobenzaldehyde (**1j**) (0.158 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.638 mL, 3.0 mmol), Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) and de-ionized H_2O (0.009 mL, 0.5 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 6 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate, coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give methyl 3-(2’-chloro-6’-fluorophenyl)-3-hydroxy-2,2-dimethylpropanoate (**3j**) in 90% purity. **3j** **3k** was purified by silica gel flash chromatography (eluent: Petroleum ether/EtOAc, 9/1) to give pure the pure compound as a colorless oil (75% yield, 0.195 g).
E-factor = 24.7
[0.158 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 0.009 g (H_2O) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.195 g (product x yield)] / 0.195 g

Mol Formula	$C_{12}H_{14}ClFO_3$	**m.p.**	Oil

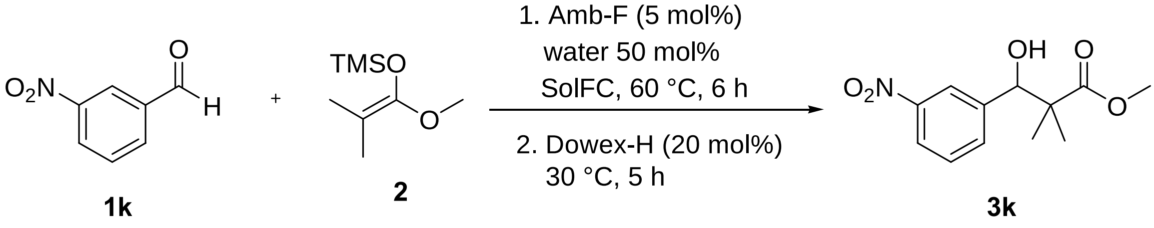
FT-IR ($CHCl_3$, cm^{-1}): 3567, 2966, 1731.

Elemental Analysis: Calcd. C, 55.29; H, 5.41; Cl, 13.60; F, 7.29; found C, 55.15; H, 5.32; Cl, 13.48; F, 7.40.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**	
	1.17	3	*d*	2	
	1.35	3	*s*		
	3.61	1	*q*	5.0	
	3.73	3	*s*		
	5.36	1	*d*	9.9	
	6.96	1	*m*		
	7.17	2	*m*		

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 20.3 ($J_{C\text{-}F}$ = 3.1), 24.2, 48.3, 52.1, 76.0, 115.0 ($J_{C\text{-}F}$ =24.3), 125.7, 125.8 ($J_{C\text{-}F}$ = 3.6), 129.4 ($J_{C\text{-}F}$ = 10.7), 134.8 ($J_{C\text{-}F}$ = 8.4), 161.7 ($J_{C\text{-}F}$ = 248.5), 176.4.

Chem. Name	**Methyl 3-hydroxy-2,2-dimethyl-3-(3’-nitrophenyl)propanoate (3k)**
Lit. Ref.	*Org. Biomol. Chem.* **2004**, *2*, 3401



Mol.Wt.: 253

METHOD:
In a screw capped vial equipped with a magnetic stirrer 3-nitrobenzaldehyde (**1k**) (0.151g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal **2**, (0.638 mL, 3.0 mmol), Amb-F(0.020 g, 0.05 mmol, 2.5 mmol/g) and distilled H_2O (0.009 mL, 0.5 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 6 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give 95% pure methyl 3-hydroxy-2,2-dimethyl-3-(3’-nitrophenyl)propanoate (**3k**) in 95% purity. **3k** was purified by silica gel flash chromatography (eluent: Petroleum ether/EtOAc, 9/1) to give pure the pure compound as a colorless oil (88% yield, 0.222 g).
E-factor = 21.5
[0.151 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 0.009 g (H_2O) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.223 g (product x yield)] / 0.223 g

Mol Formula	$C_{12}H_{15}NO_5$	**m.p.**	Oil

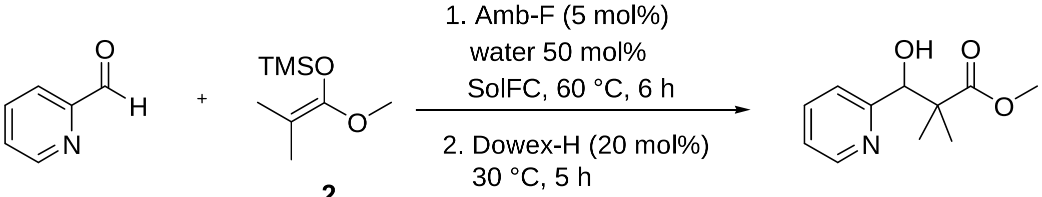
FT-IR ($CHCl_3$, cm^{-1}): 3599, 2986, 1711.

Elemental Analysis: Calcd. C, 56.91; H, 5.97; N, 6.53; found C, 60.04; H, 5.80; N, 6.42.

	δ value	**No. H**	**Mult.**	**j value/Hz**
^{1}H NMR 400 MHz $CDCl_3$	1.11	3	*m*	
	1.38	3	*m*	
	3.47	1	*bs*	
	3.72	3	*s*	
	4.99	1	*s*	
	7.50	1	*t*	7.9
	7.63	1	*d*	7.7
	8.12	1	*d*	8.3
	8.16	1	*m*	

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 19.2, 22.4, 47.6, 52.2, 77.5, 122.4, 122.6, 128.6, 133.6, 142.0, 147.8, 177.5.

Chem. Name	**Methyl 3-hydroxy-2,2-dimethyl-3’-pyridin-2’-ylpropanoate (3l)**
Lit. Ref.	*Tetrahedron*, **2000**, *56*, 7309.



1l **2** **3l**

Mol.Wt.: 209

METHOD:
In a screw capped vial equipped with a magnetic stirrer pyridine-2-carbaldehyde (**1l**) (0.107 g, 1.0mmol), methyl trimethylsilyl dimethylketene acetal **2**, (0.638 mL, 3.0 mmol), Amb-F(0.020 g, 0.05 mmol, 2.5 mmol/g) and distilled H_2O (0.009 mL, 0.5 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 6 hours THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O (2 x 2 mL). Organic layer was dried over sodium sulfate/potassium carbonate (2:1 mixture). Both methyl 2-methylpropionate , coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure methyl 3-hydroxy-2,2-dimethyl-3-pyridin-2-ylpropanoate (**3l**) as a colorless oil (93% yield, 0.194 g).
E-factor = 24.6
[0.107 g (aldehyde) + 0.273 g (methyl trimethylsilyl dimethylketene acetal) + 0.009 g (H_2O) + 1.78 g (THF) + 2.8 g (Et_2O extraction 2 x 2 mL) – 0.194 g (product x yield)] / 0.194 g

Mol Formula	$C_{11}H_{15}NO_3$	**m.p.**	Oil

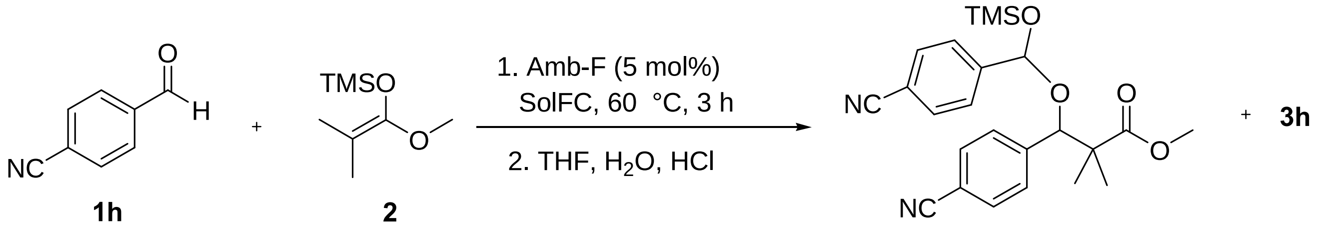
FT-IR ($CHCl_3$, cm^{-1}): 3017, 2986, 1716.

Elemental Analysis: Calcd. C, 63.14; H, 7.23; N, 6.69; found C, 63.21; H, 7.15; N, 6.72.

^{1}H NMR 400 MHz $CDCl_3$	**δ value**	**No. H**	**Mult.**	**j value/Hz**
	1.06	3	*s*	
	1.14	3	*s*	
	3.69	3	*s*	
	4.65	1	*d*	6.9
	4.92	1	*d*	6.4
	7.17	2	*m*	
	7.62	1	*t*	7.7
	8.51	1	*d*	4.6

^{13}C NMR (100.6 MHz, $CDCl_3$) δ : 20.7, (one carbon is missing) 48.3, 51.8, 76.9, 122.0, 122.7, 136.0, 148.0, 158.3, 177.0.

Chem. Name	**Methyl 3-(4'-cyanophenyl)-3-{(4'-cyanophenyl)[(trimethylsilyl)oxy]methoxy}-2,2-dimethylpropanoate (6h)**
Lit. Ref.	---



1h **2** **6h**

Mol.Wt.: 437

METHOD:
In a screw capped vial equipped with a magnetic stirrer 4-cyanobenzaldehyde (**1h**) (0.131 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal **2**, (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol/g) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 hours the crude mixture was diluted with Petroleum ether, the catalyst was filtered off and **6h** purified by column chromatography on neutral alumina (eluent: Petroleum ether/EtOAc, 95/5). **6h** was obtained as a diasteromeric mixture.(1:0.78).

Mol Formula	$C_{24}H_{28}N_2O_4Si$	**m.p.**	Oil

FT-IR ($CHCl_3$, cm^{-1}): 3015, 2955, 2232, 1713.

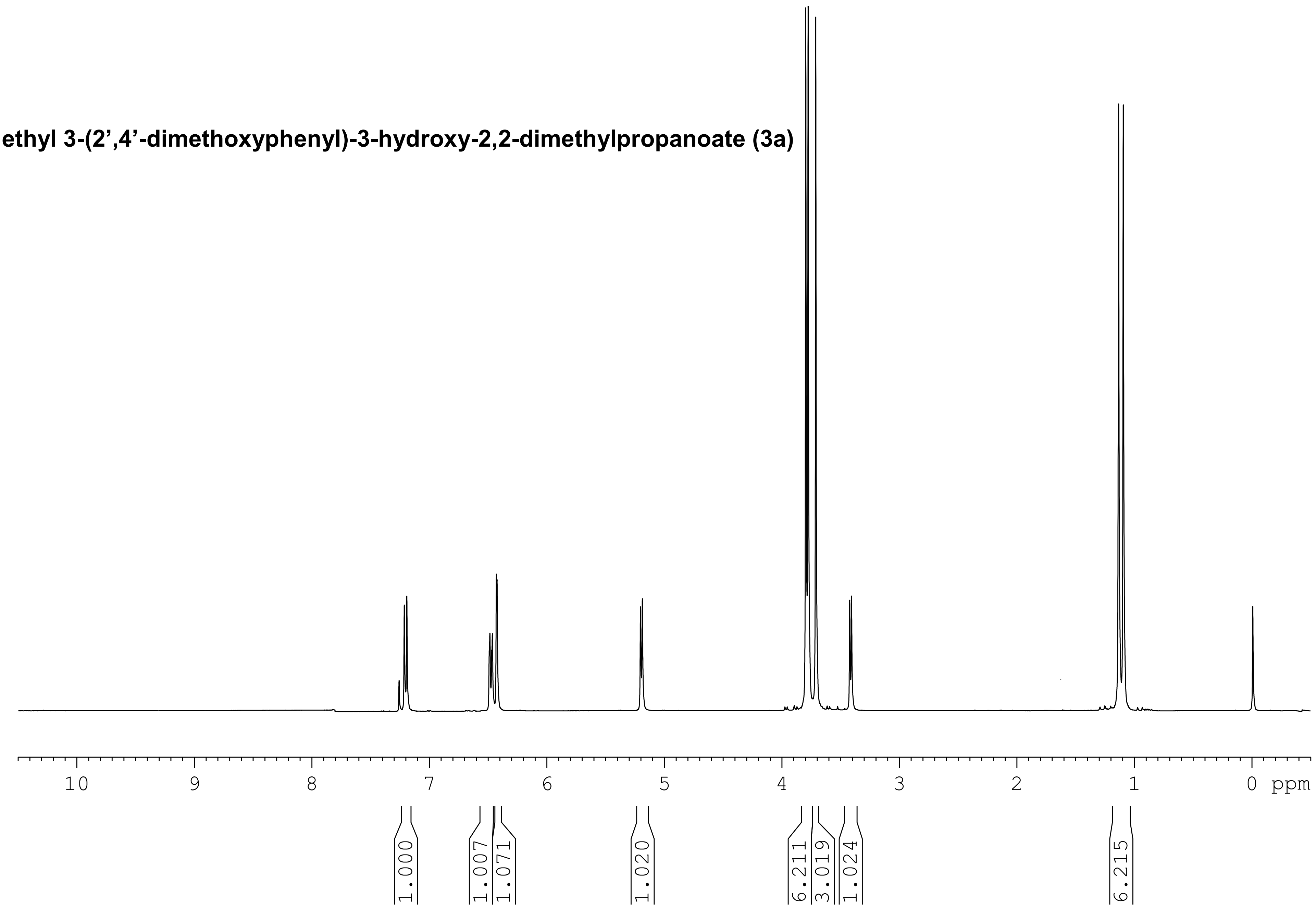
Elemental Analysis: Calcd. C, 66.03; H, 6.46; N, 6.42; Si, 6.43 found C, 66.20; H, 6.28; N,6.25; Si, 6.58.

^{1}H NMR 400 MHz $CDCl_3$ major diasteroisomer	**δ value**	**No. H**	**Mult.**	**j value/Hz**
	-0.18	9	*s*	
	0.97	3	*s*	
	1.05	3	*s*	
	3.60	3	*s*	
	4.86	1	*s*	
	5.69	1	*s*	
minor diasteroisomer	-0.12	9	*s*	
	1.00	3	*s*	
	1.15	3	*s*	
	3.66	3	*s*	
	5.09	1	*s*	
	5.33	1	*s*	

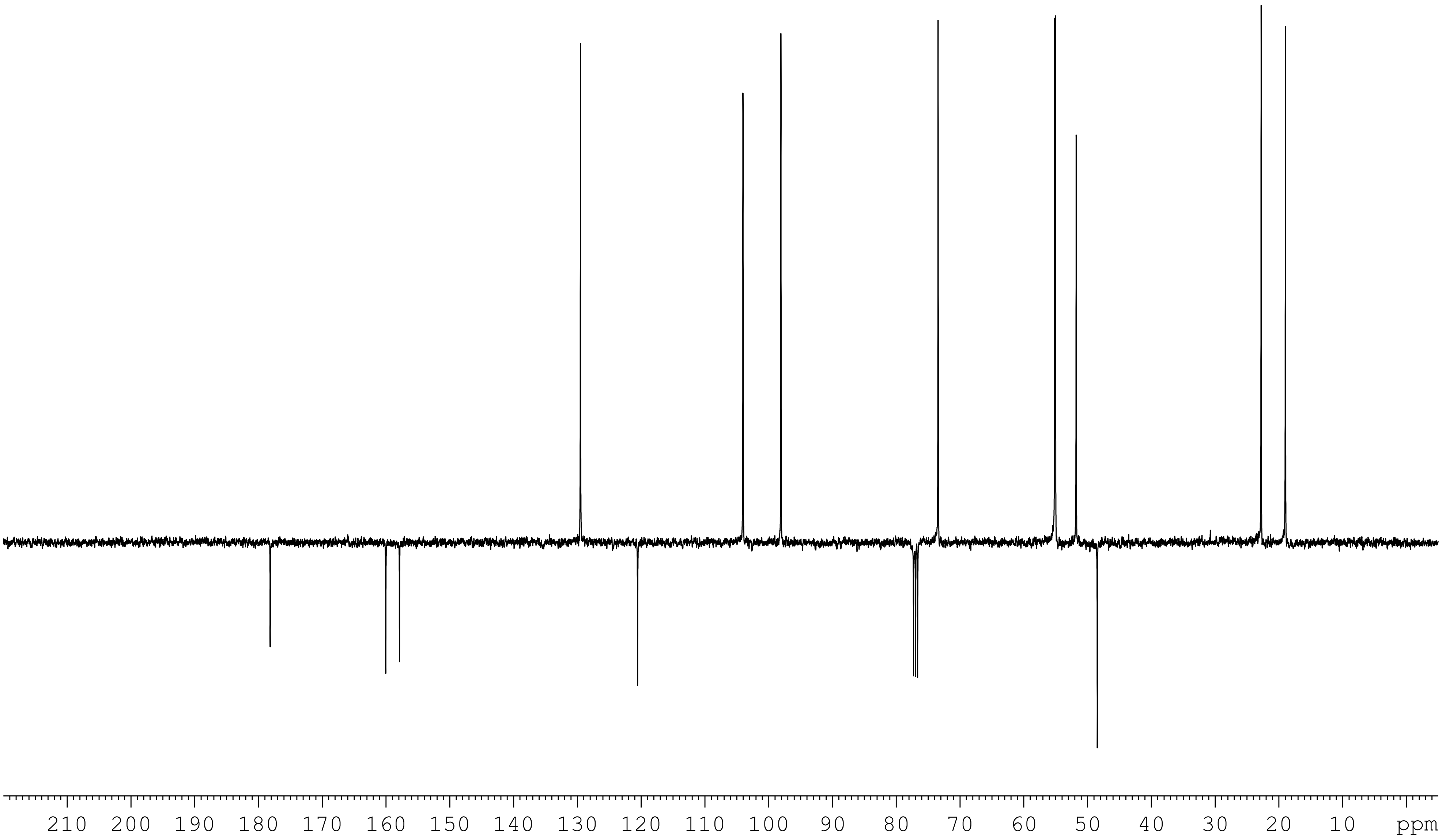
^{13}C NMR (100.6 MHz, $CDCl_3$) δ : (major diasteroisomer) -0.2, 18.7, 22.2, 48.1, 84.0, 98.3
(minor diasteroisomer) -0.03, 20.4, 20.9, 47.7, 80.1, 93.7

Copies of ^{1}H NMR and ^{13}C NMR spectra directly converted to PDF files from Bruker Top Spin software

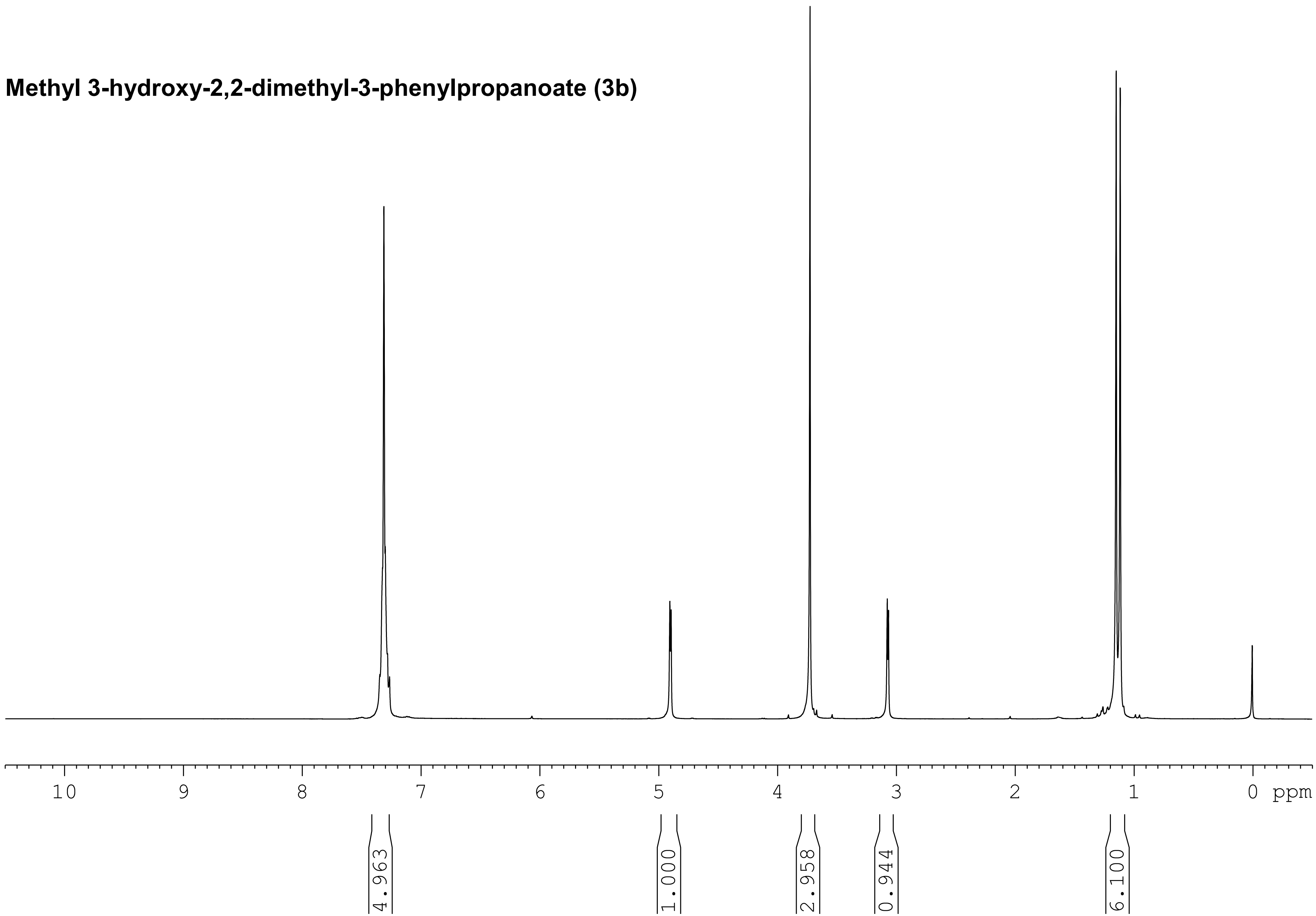
Methyl 3-(2’,4’-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (3a)



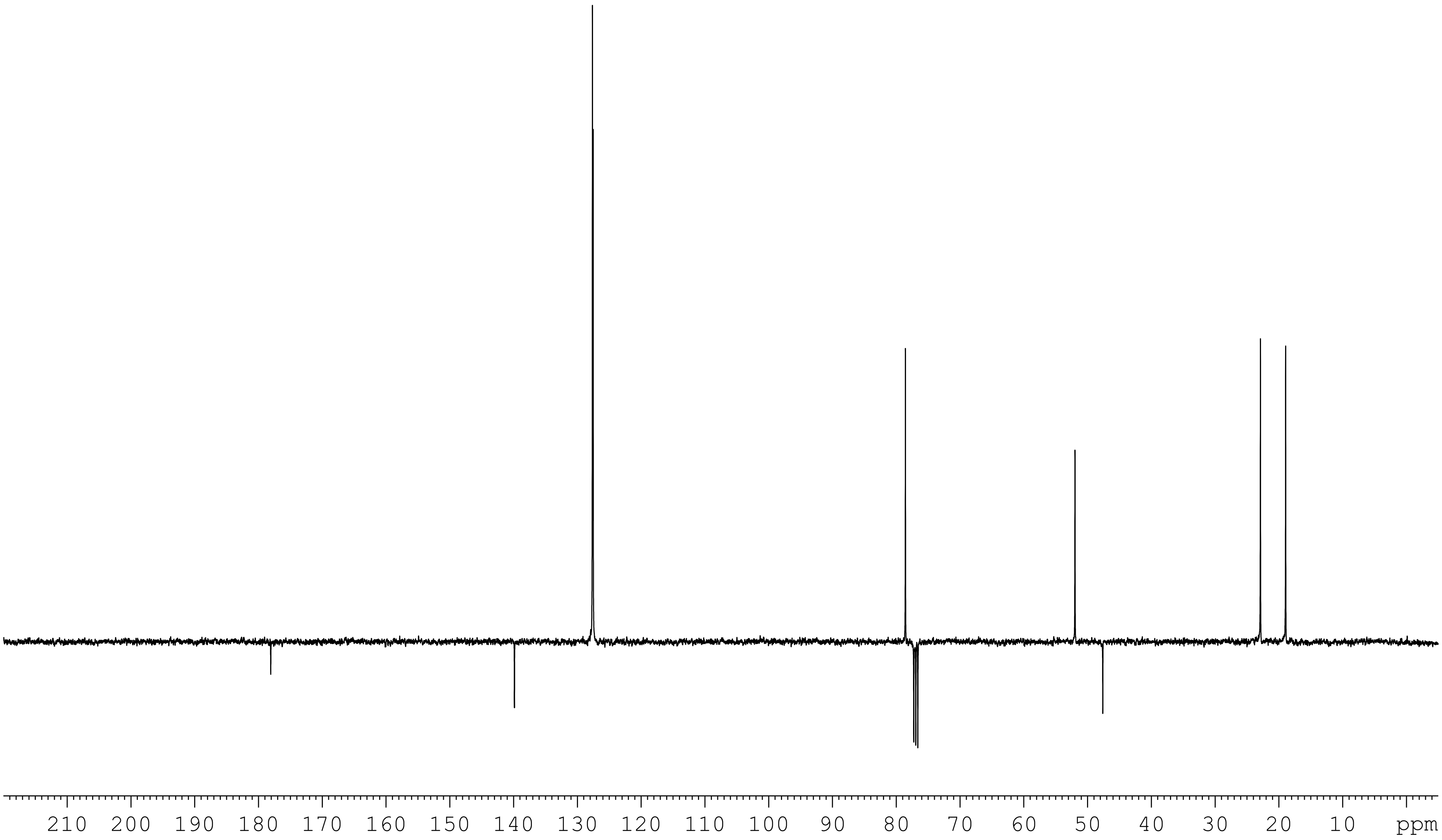
Methyl 3-(2’,4’-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (3a)



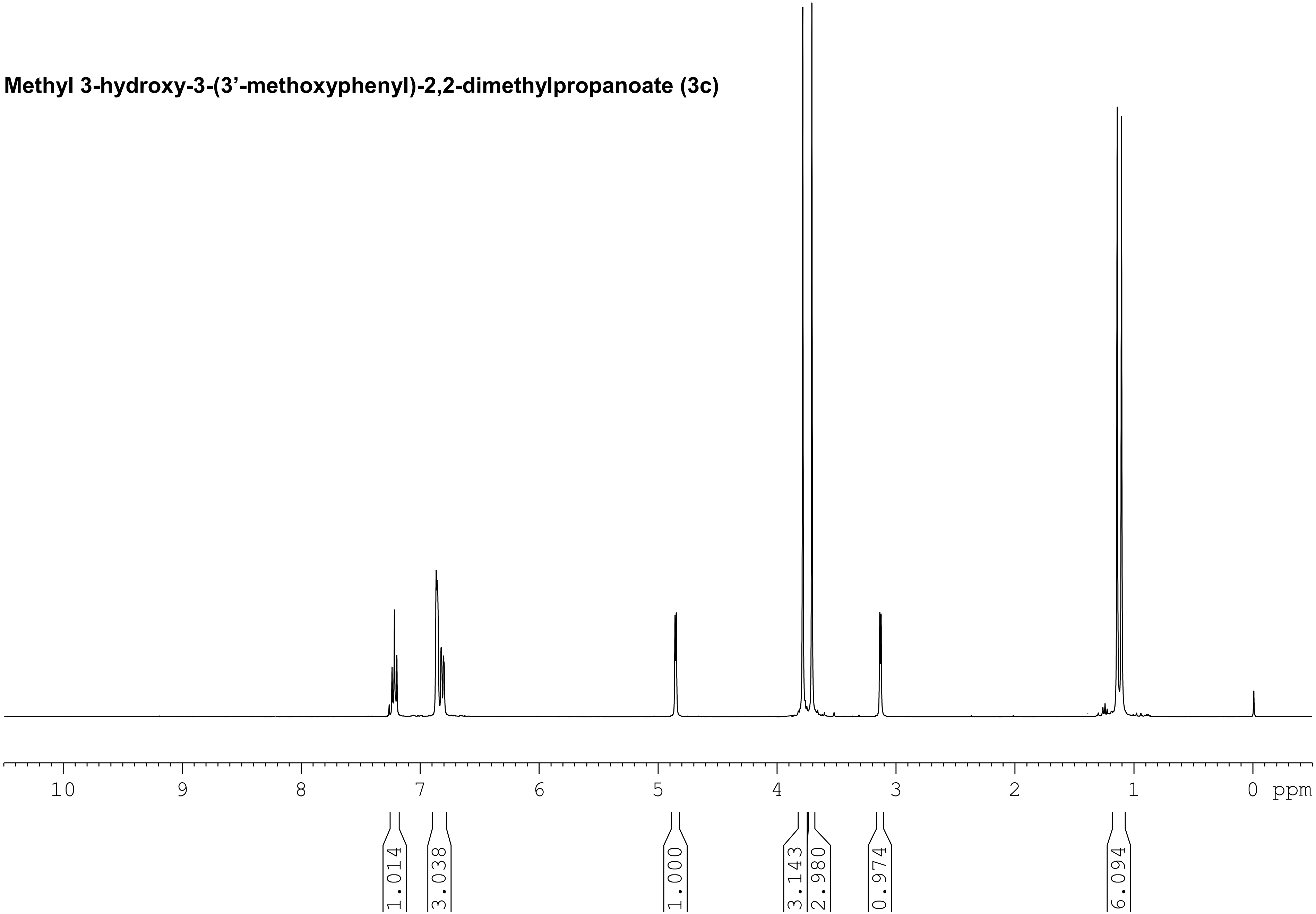
Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (3b)



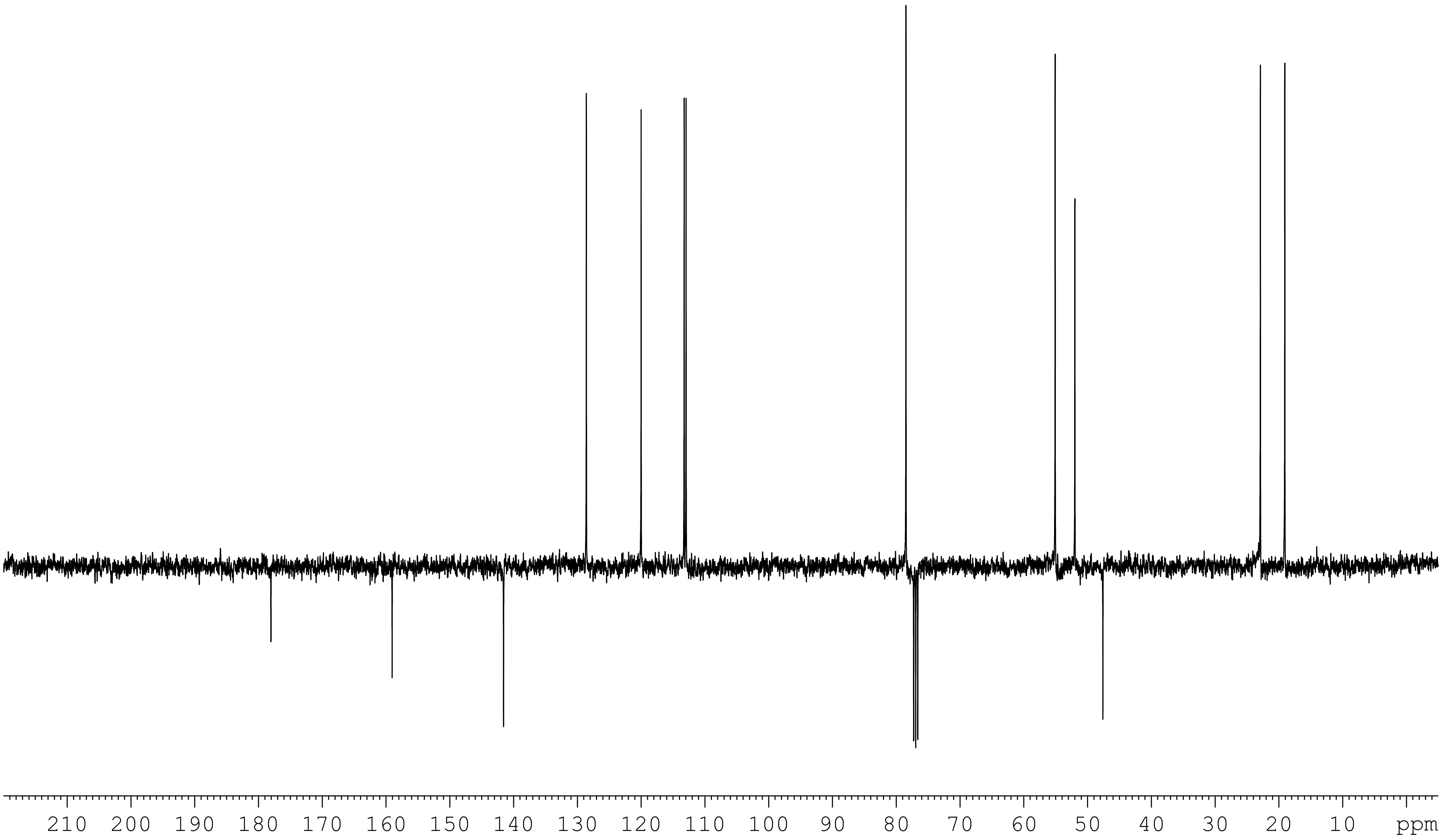
Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (3b)



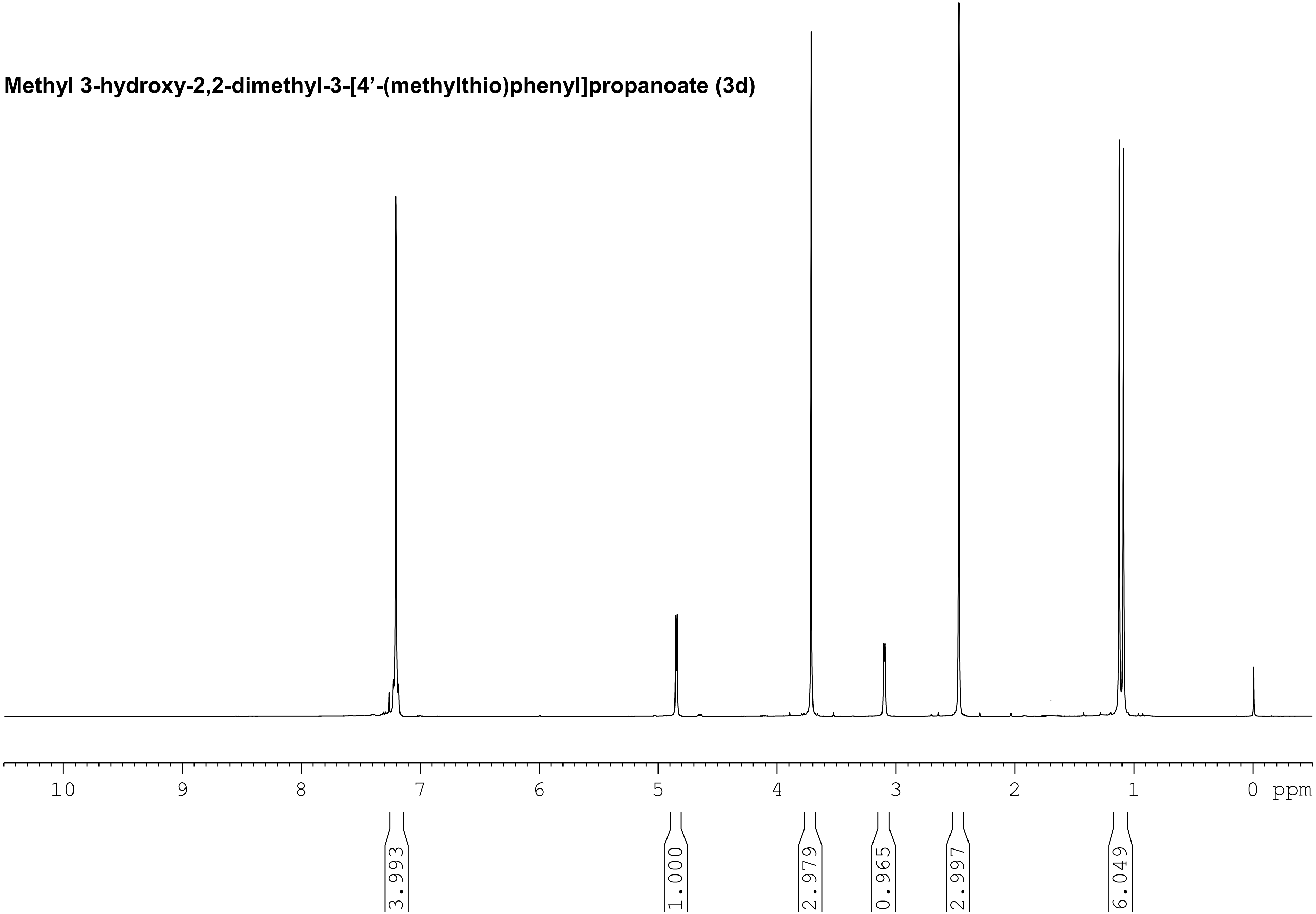
Methyl 3-hydroxy-3-(3’-methoxyphenyl)-2,2-dimethylpropanoate (3c)



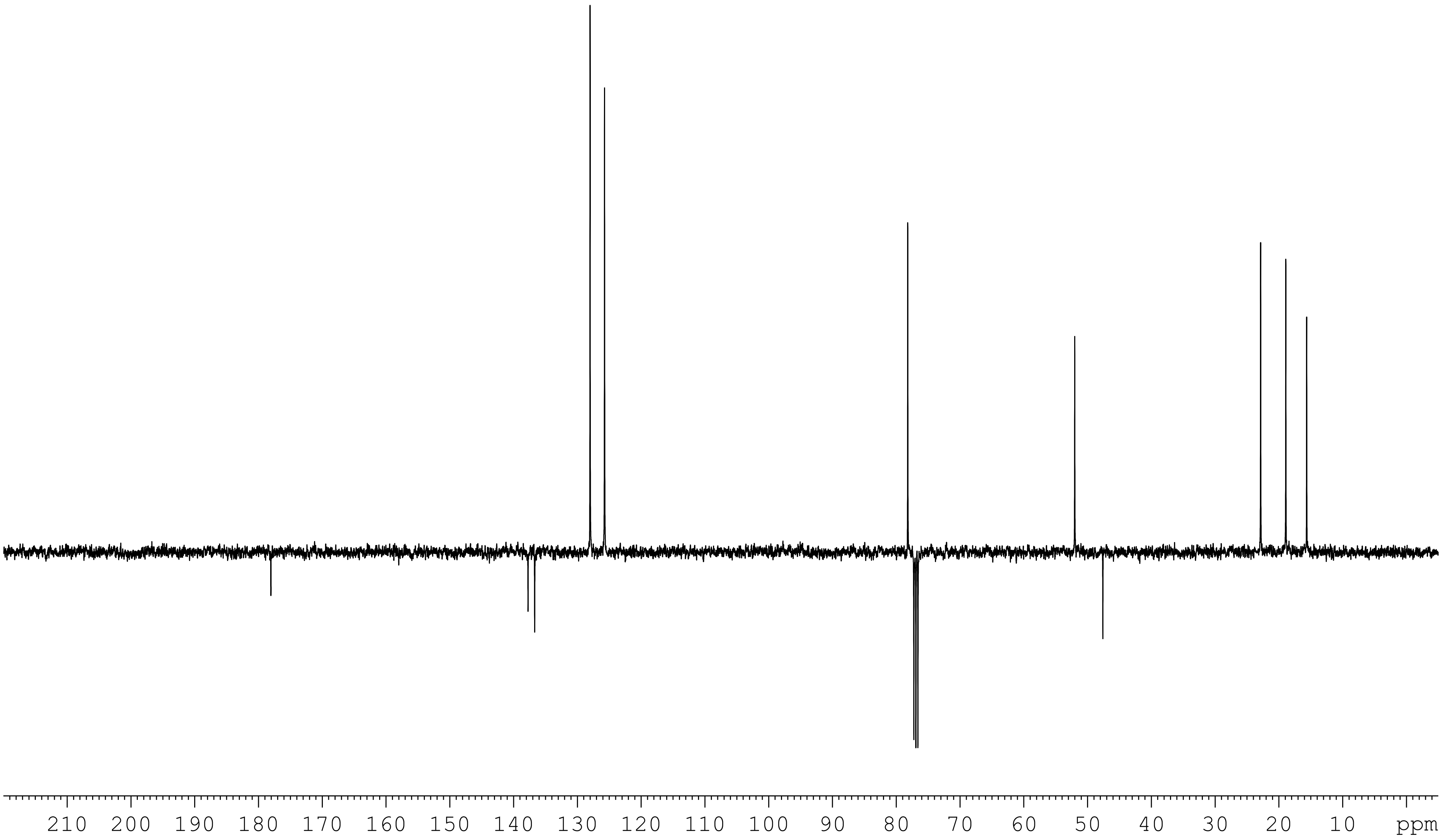
Methyl 3-hydroxy-3-(3’-methoxyphenyl)-2,2-dimethylpropanoate (3c)



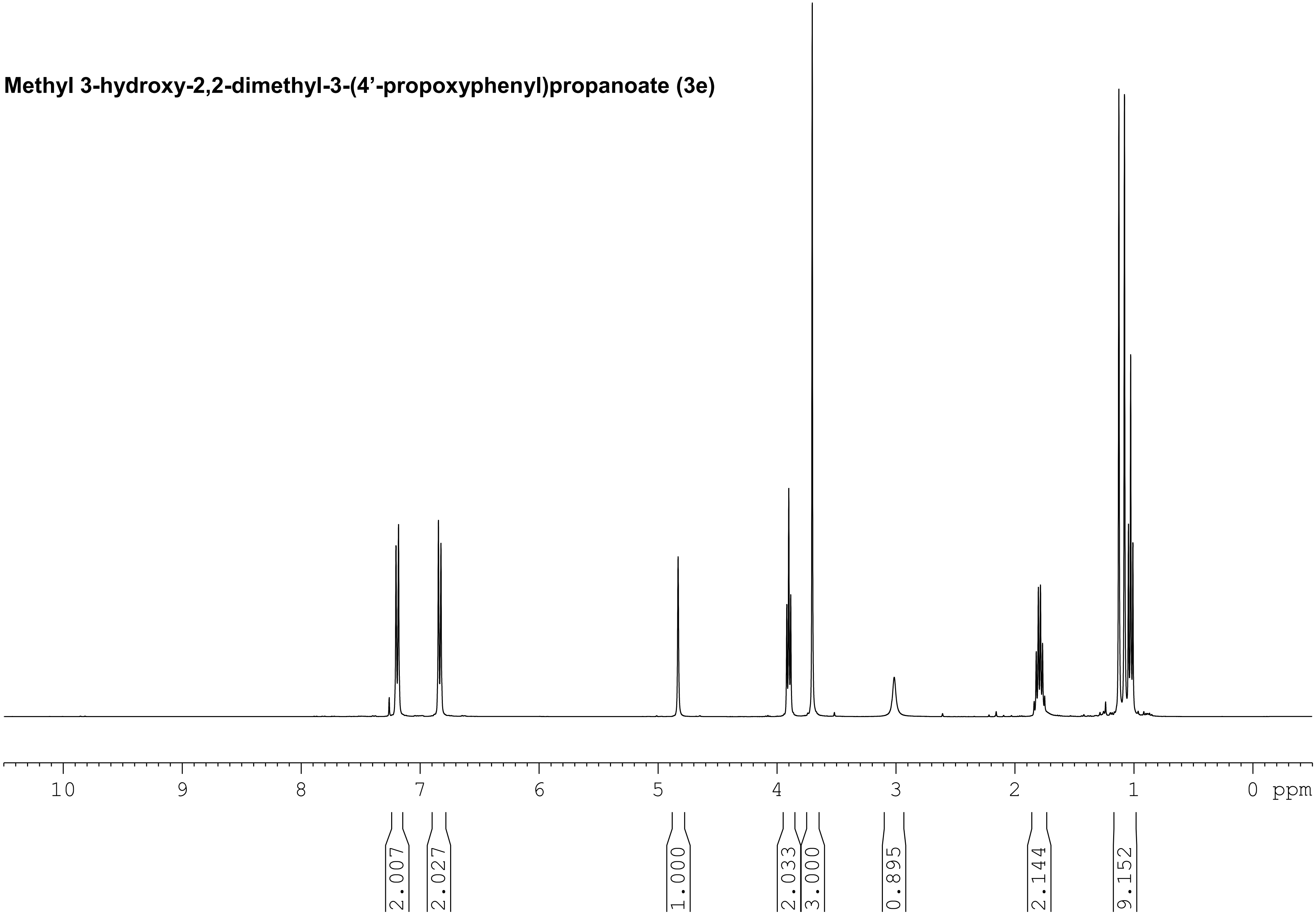
Methyl 3-hydroxy-2,2-dimethyl-3-[4'-(methylthio)phenyl]propanoate (3d)



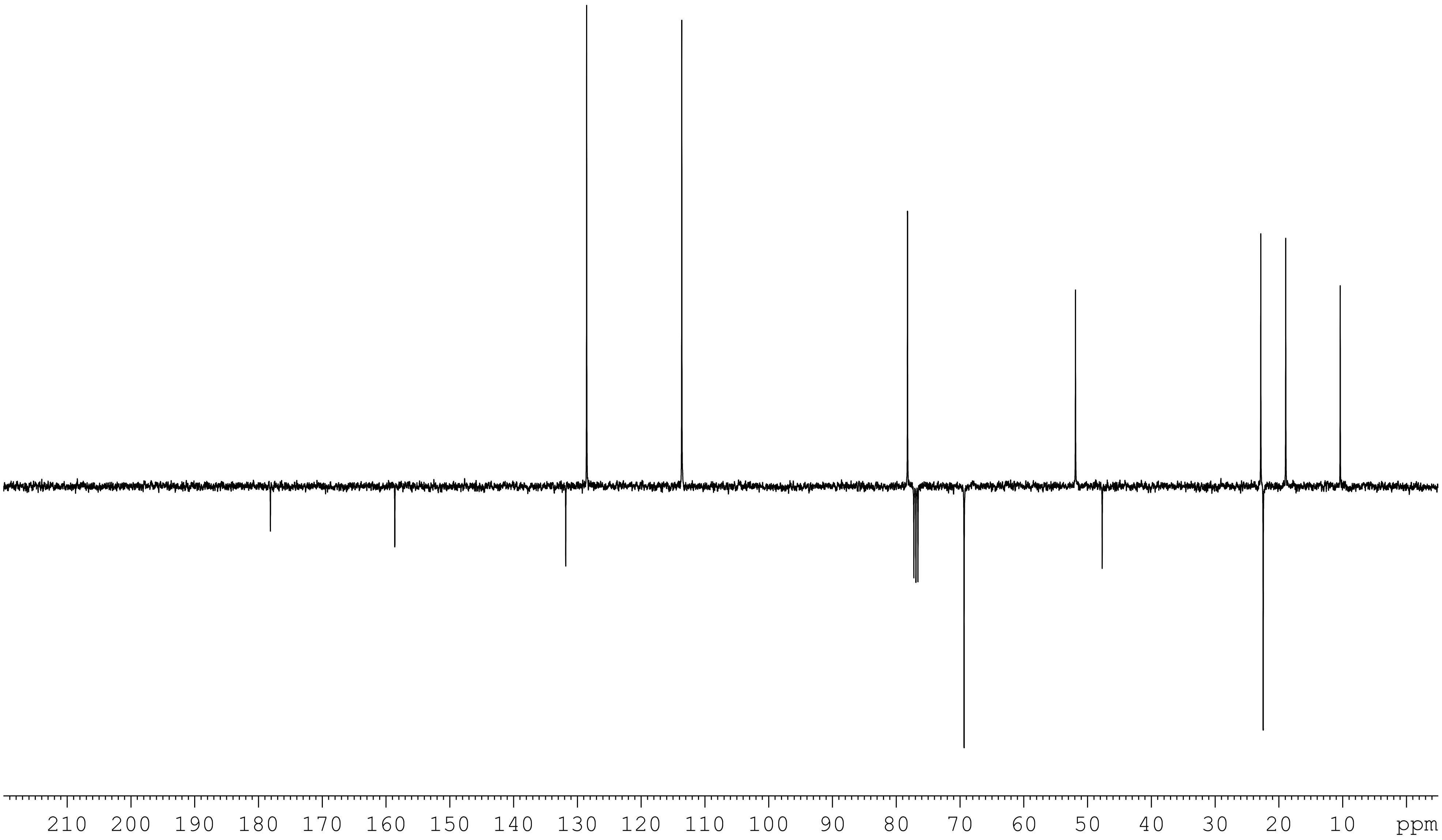
Methyl 3-hydroxy-2,2-dimethyl-3-[4’-(methylthio)phenyl]propanoate (3d)



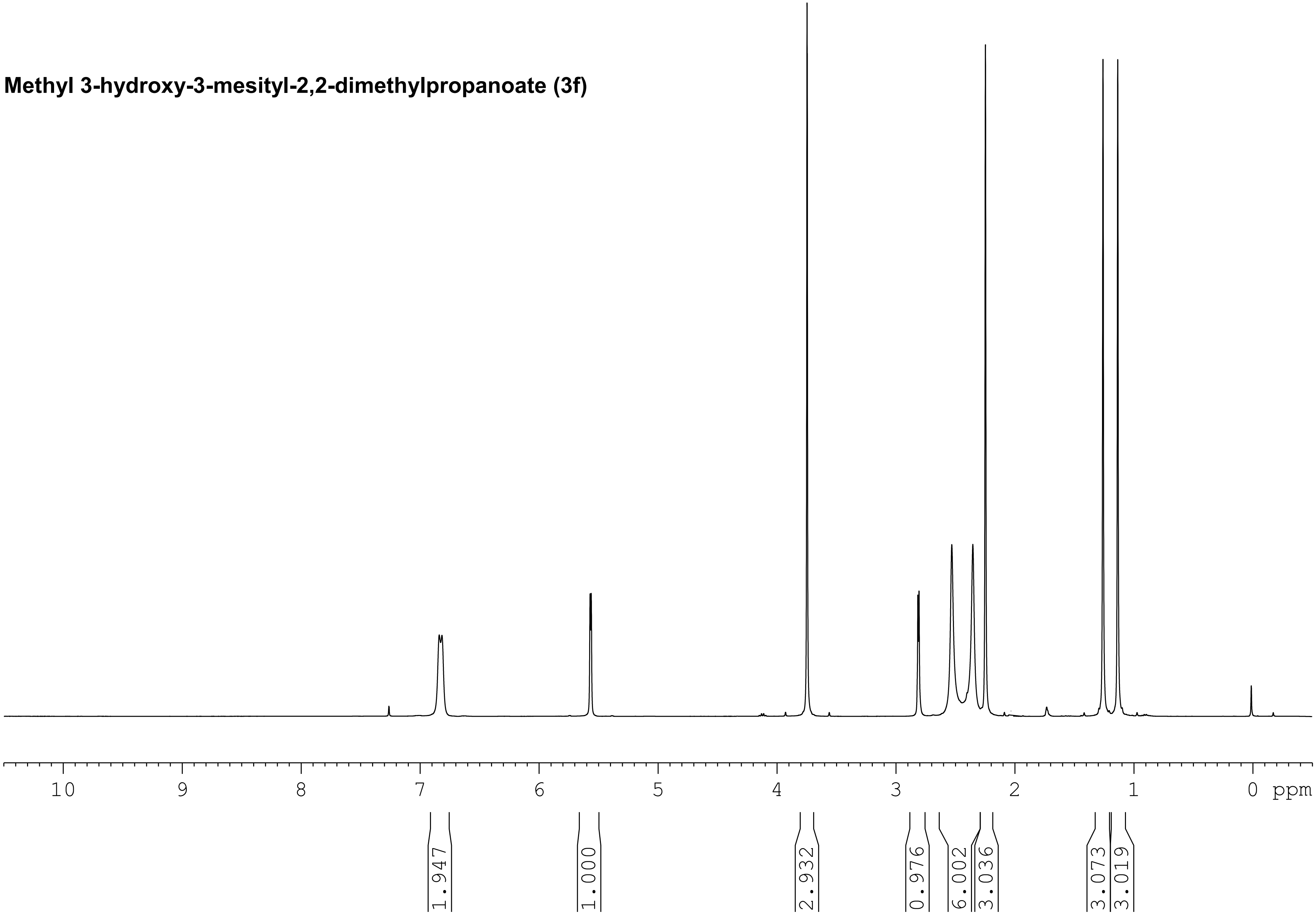
Methyl 3-hydroxy-2,2-dimethyl-3-(4'-propoxyphenyl)propanoate (3e)



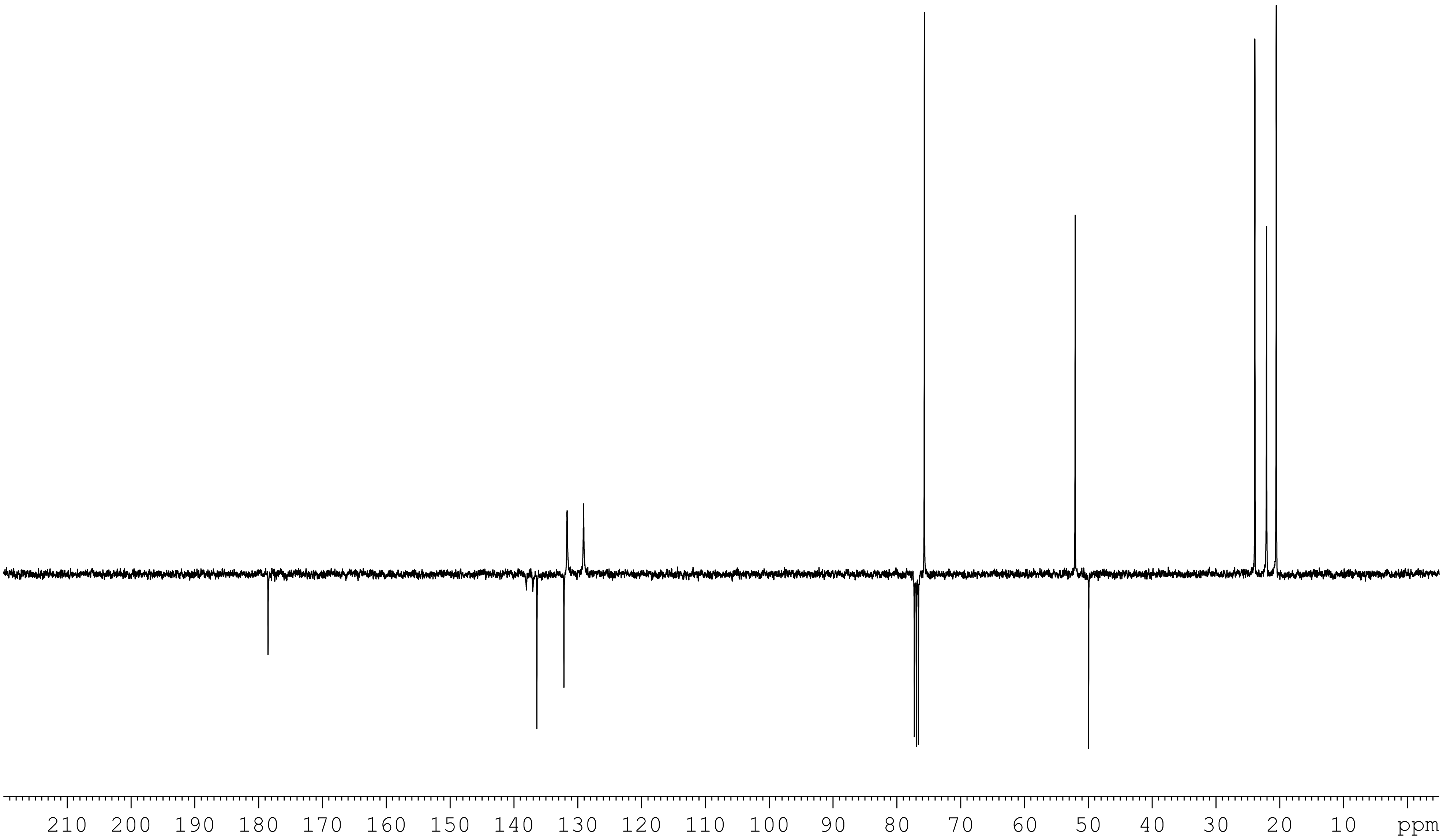
Methyl 3-hydroxy-2,2-dimethyl-3-(4’-propoxyphenyl)propanoate (3e)



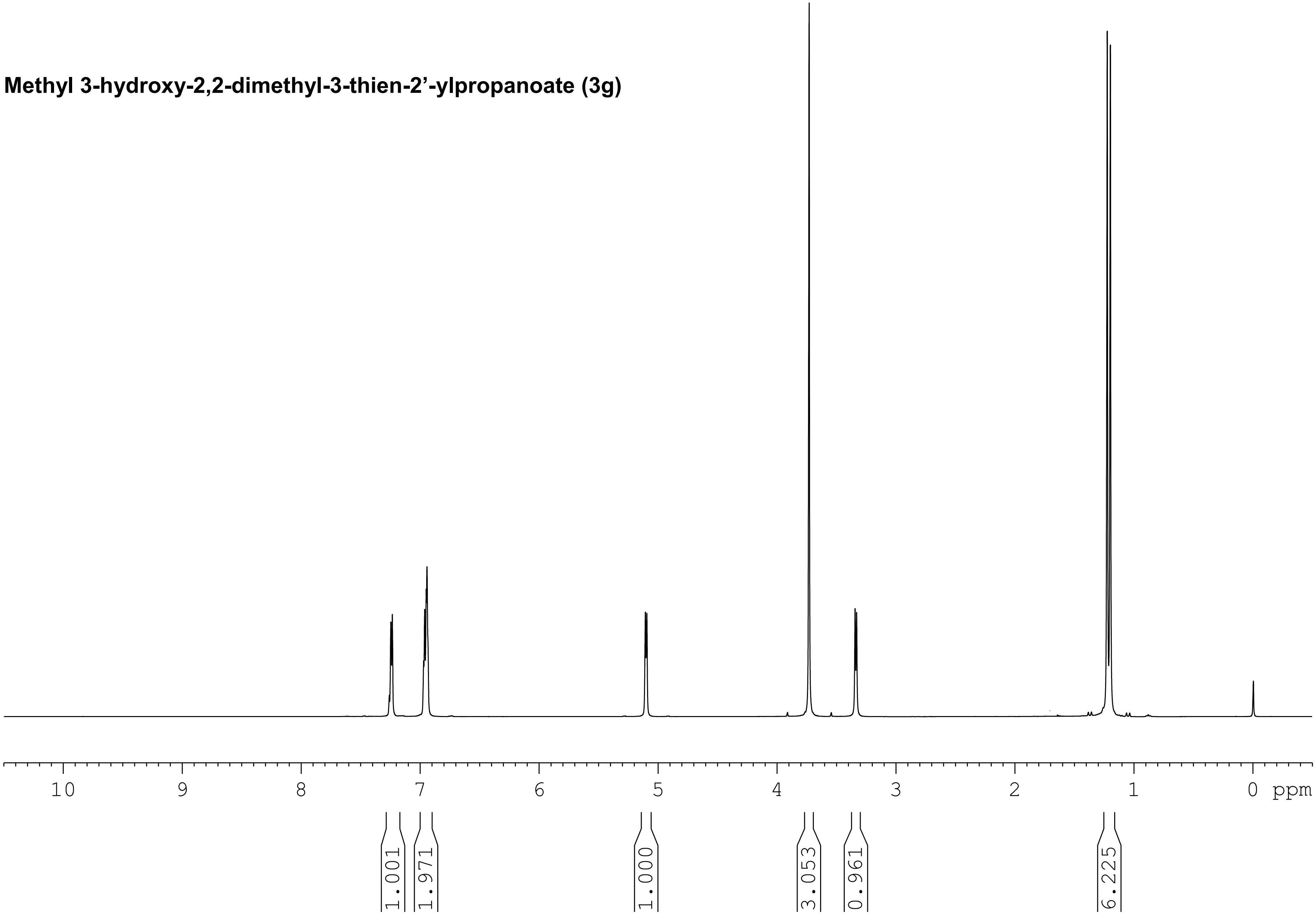
Methyl 3-hydroxy-3-mesityl-2,2-dimethylpropanoate (3f)



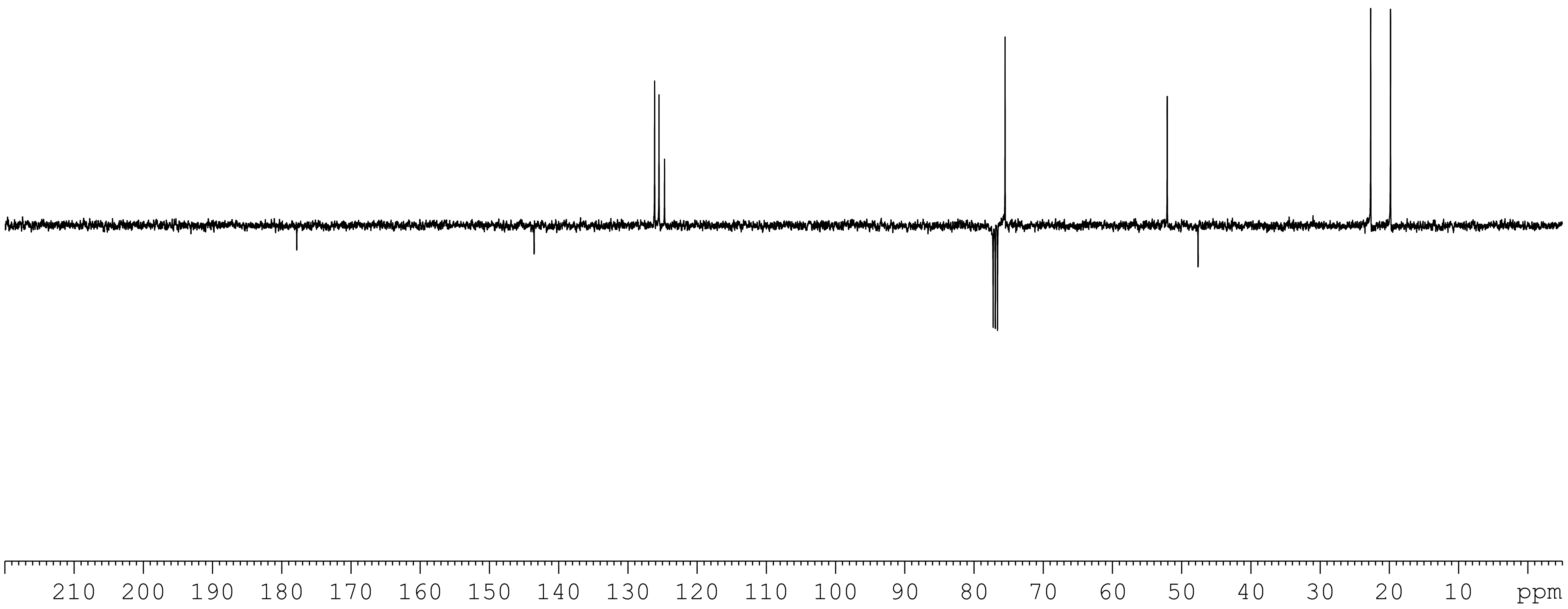
Methyl 3-hydroxy-3-mesityl-2,2-dimethylpropanoate (3f)



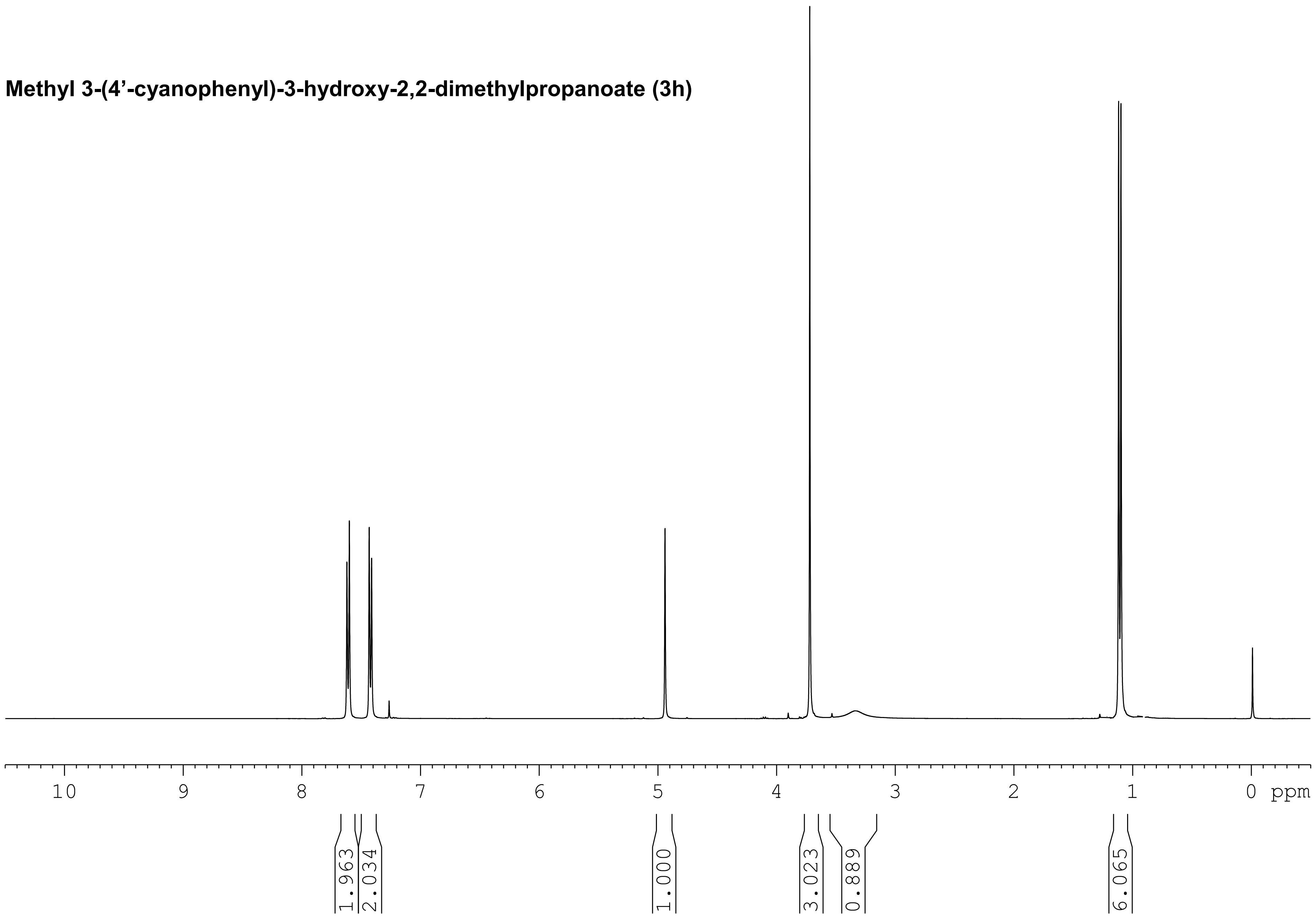
Methyl 3-hydroxy-2,2-dimethyl-3-thien-2’-ylpropanoate (3g)



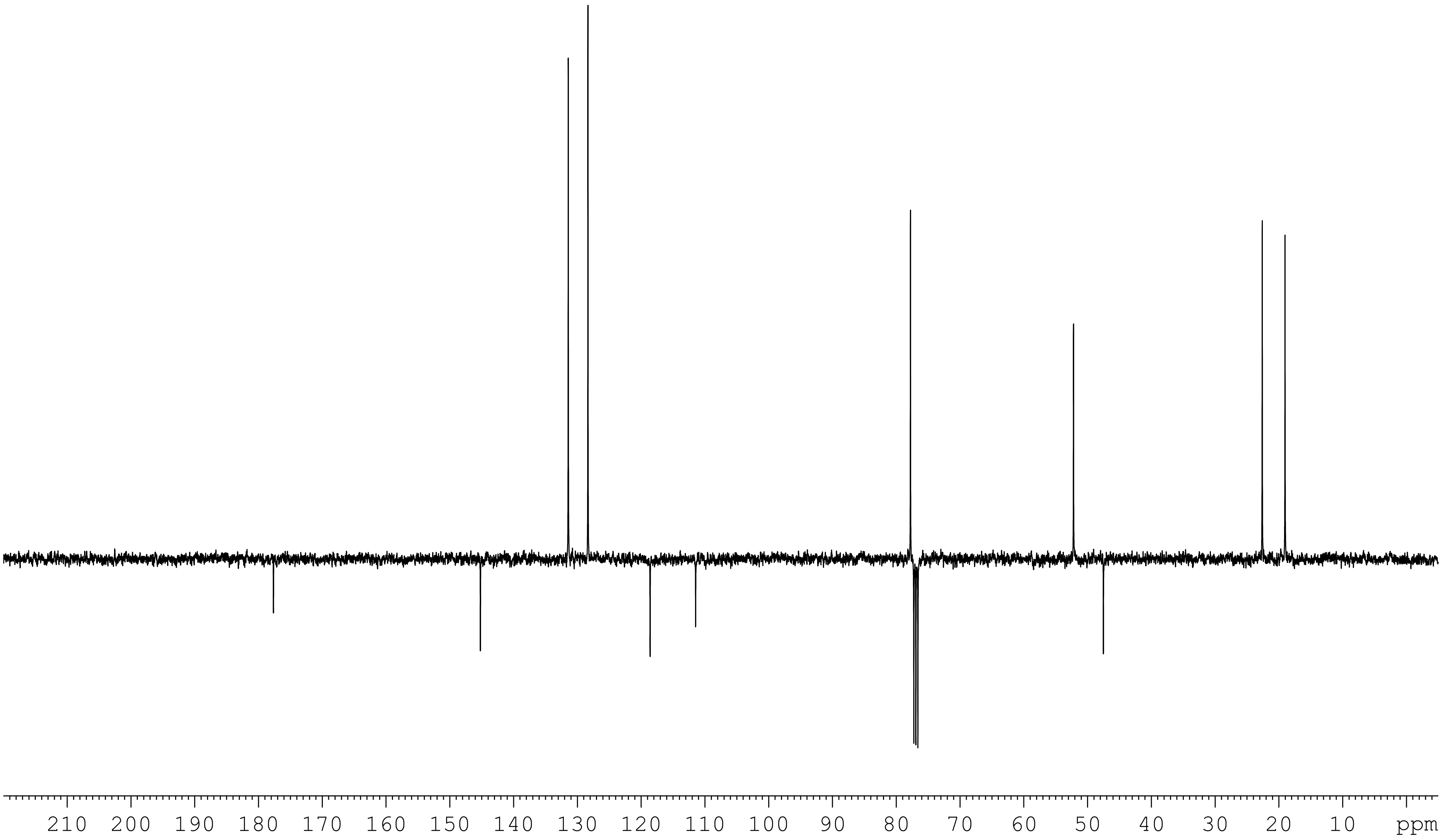
Methyl 3-hydroxy-2,2-dimethyl-3-thien-2’-ylpropanoate (3g)



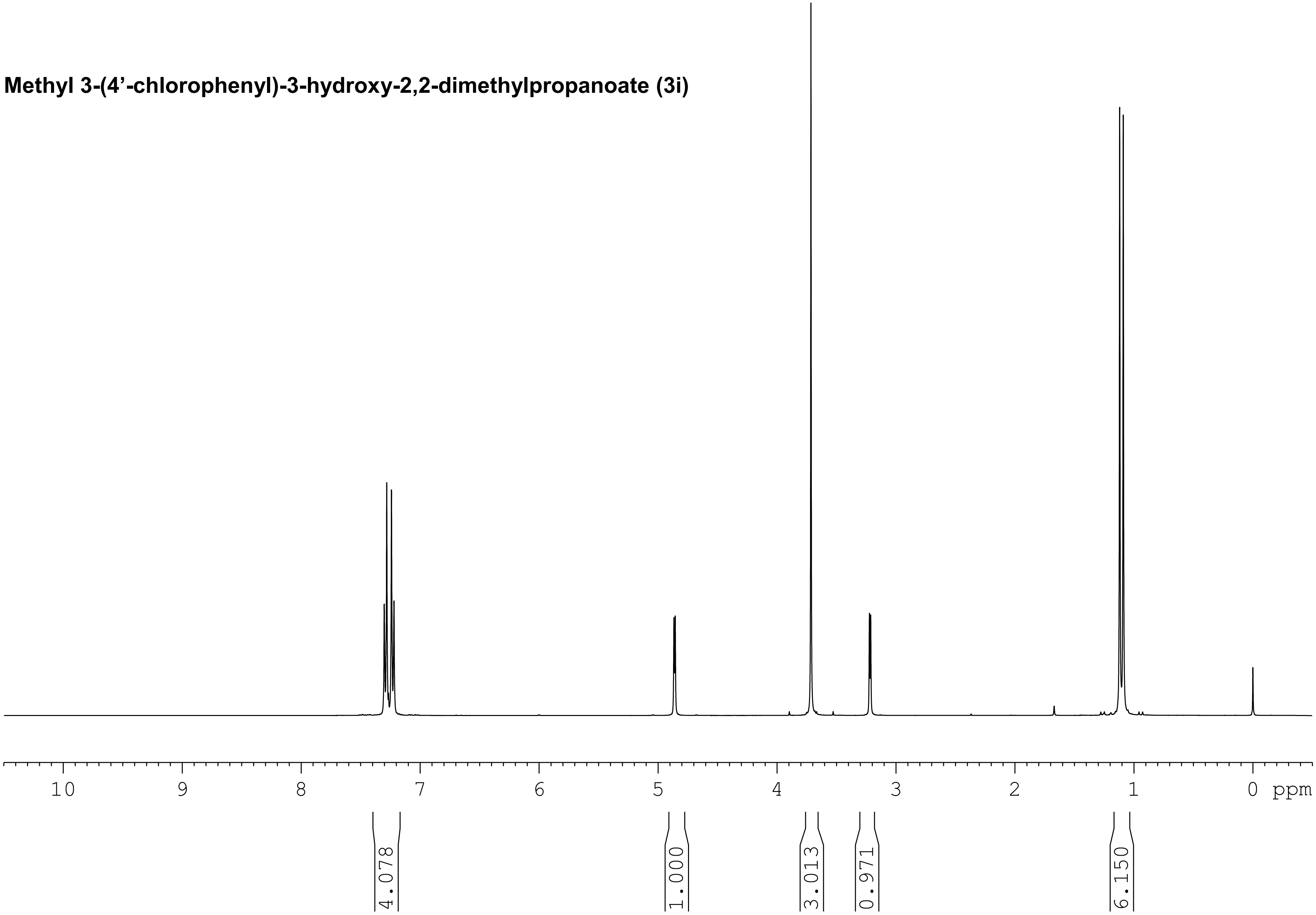
Methyl 3-(4’-cyanophenyl)-3-hydroxy-2,2-dimethylpropanoate (3h)



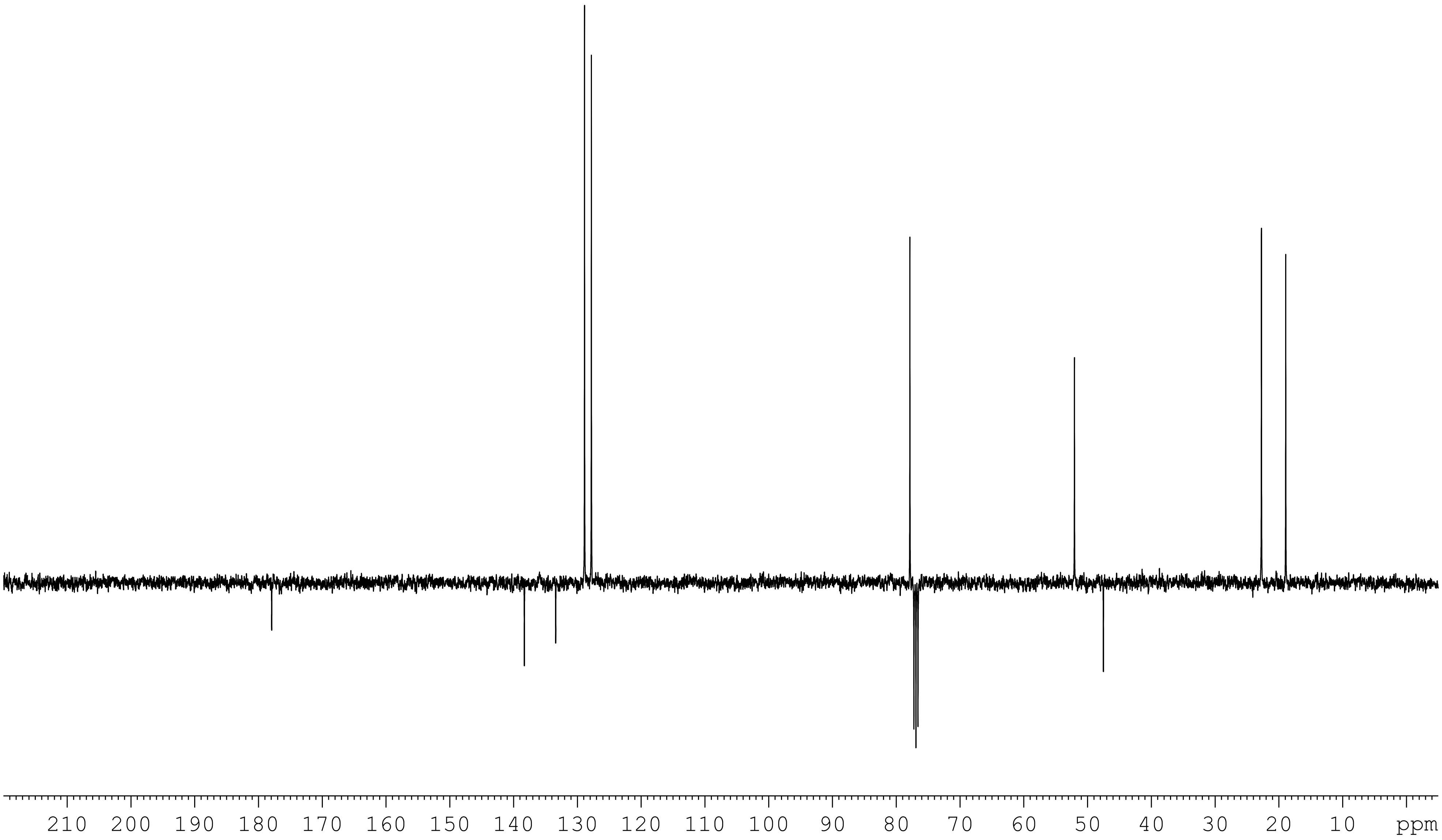
Methyl 3-(4’-cyanophenyl)-3-hydroxy-2,2-dimethylpropanoate (3h)



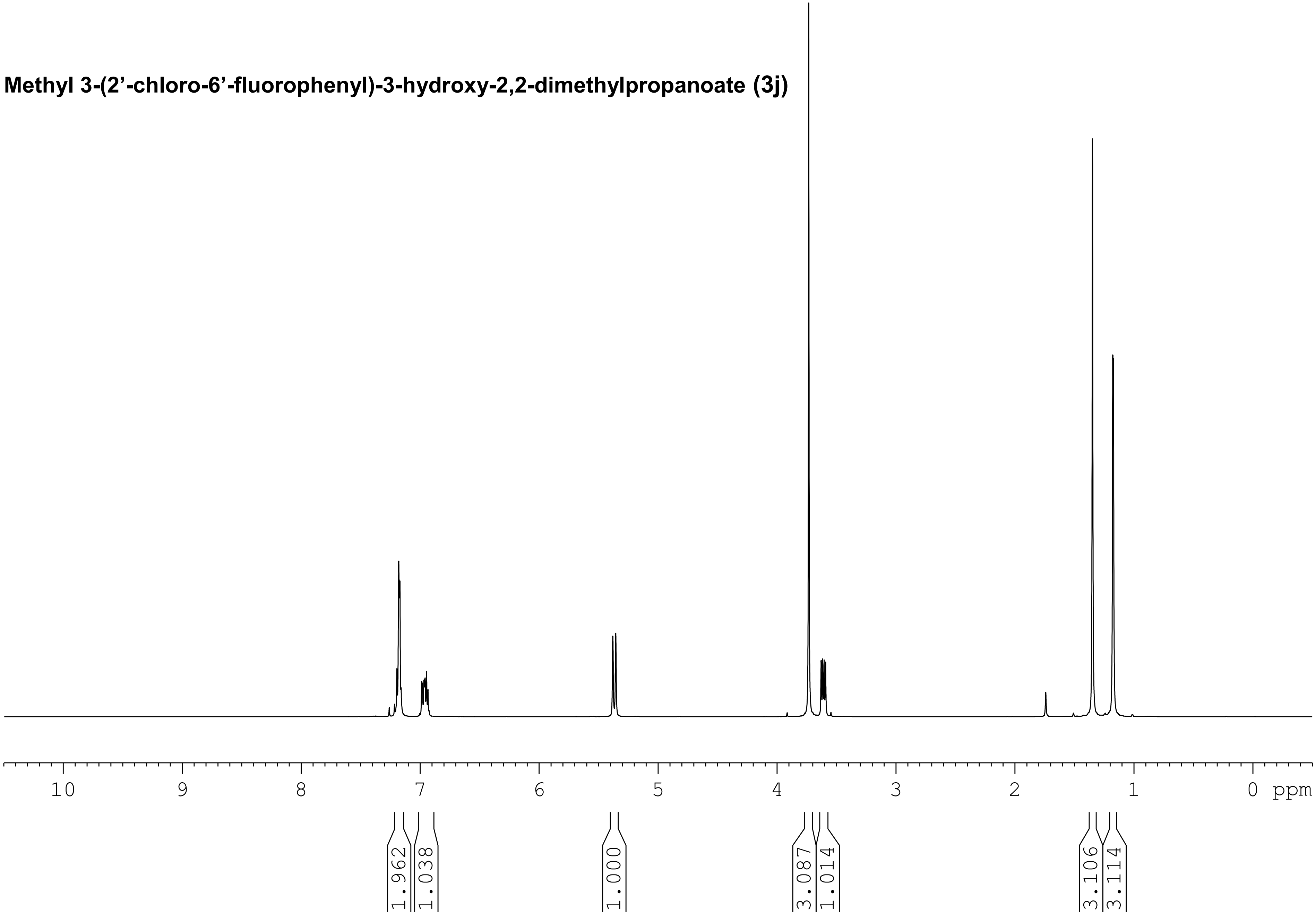
Methyl 3-(4'-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate (3i)



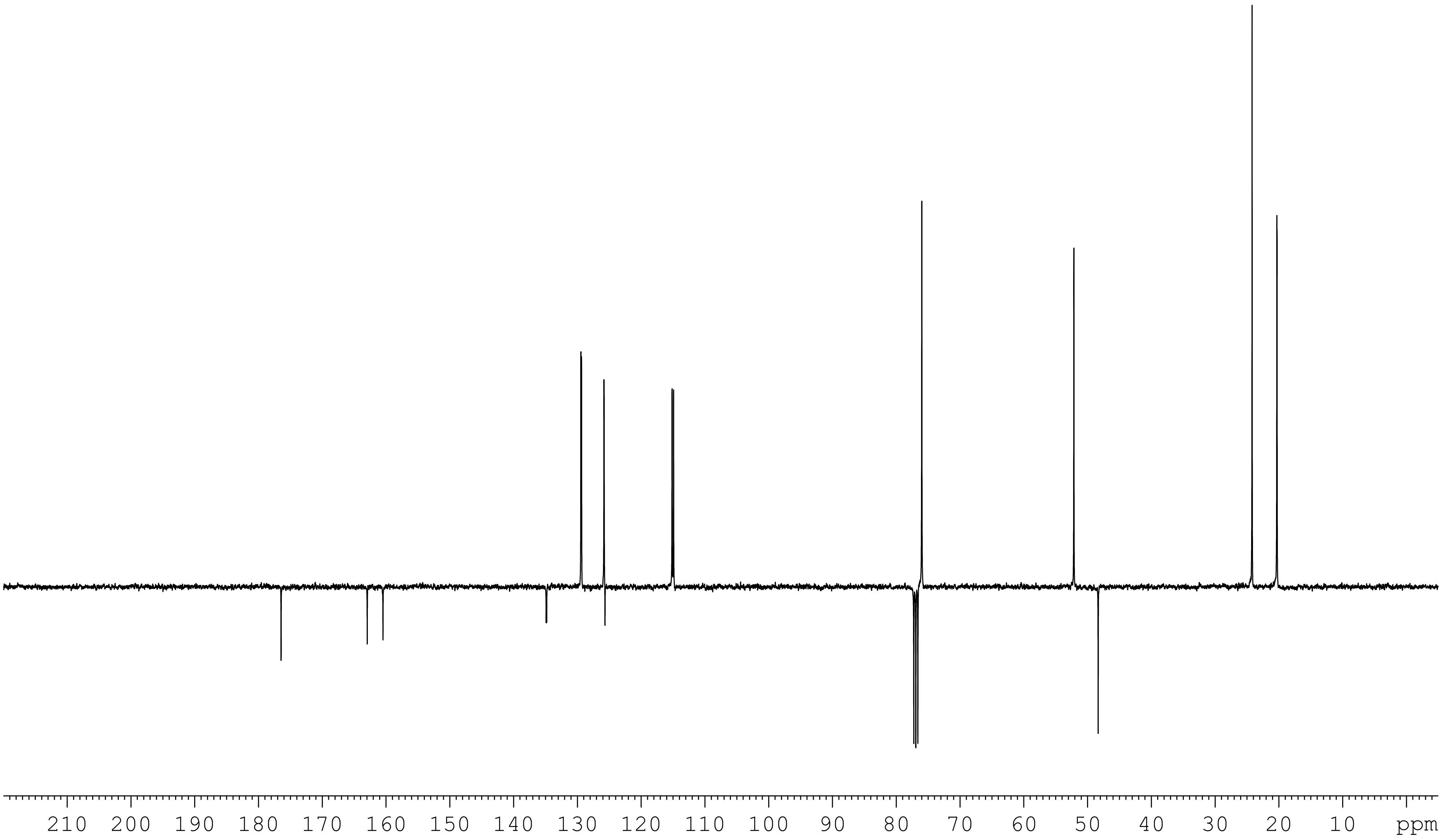
Methyl 3-(4’-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate (3i)



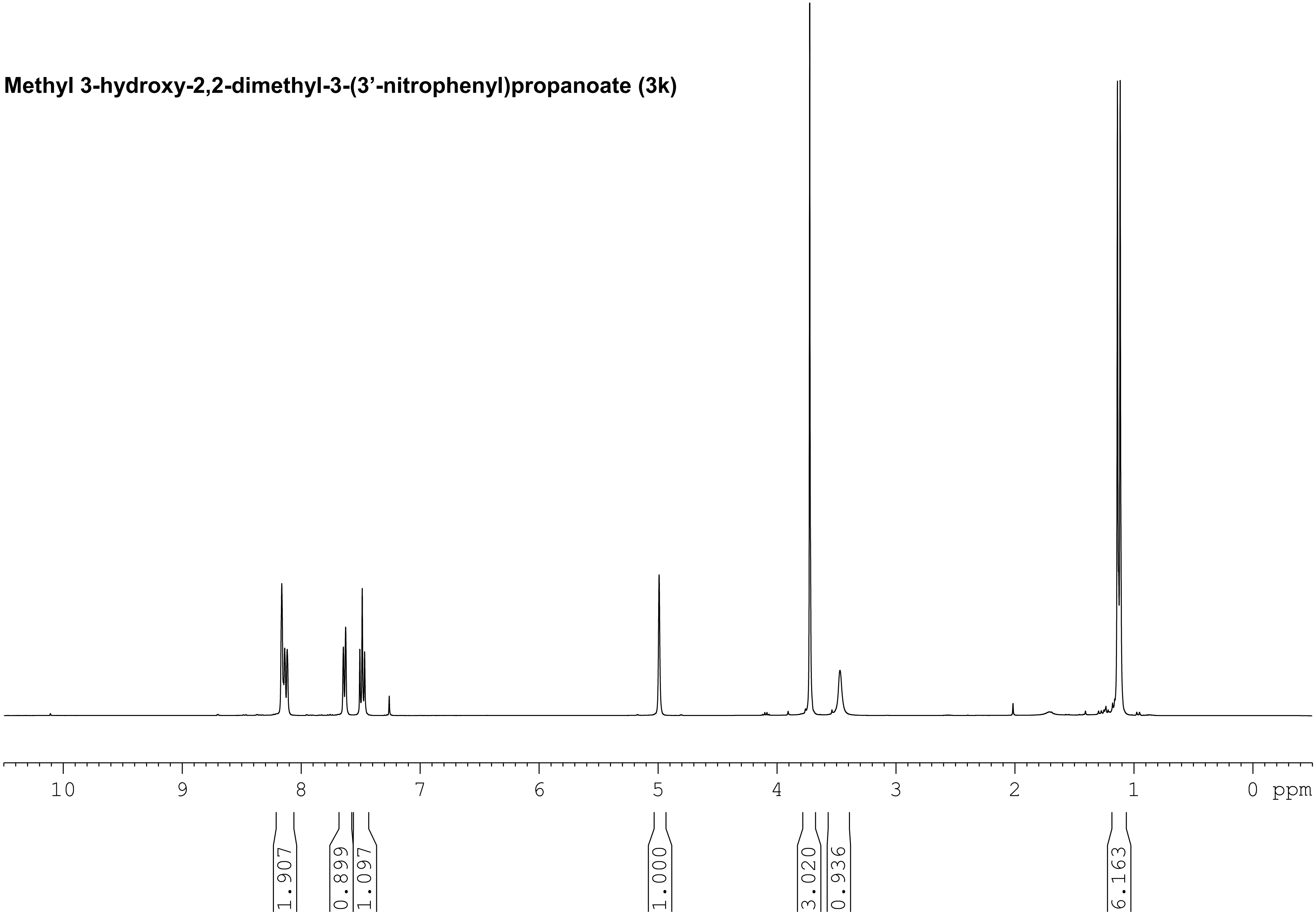
Methyl 3-(2'-chloro-6'-fluorophenyl)-3-hydroxy-2,2-dimethylpropanoate (3j)



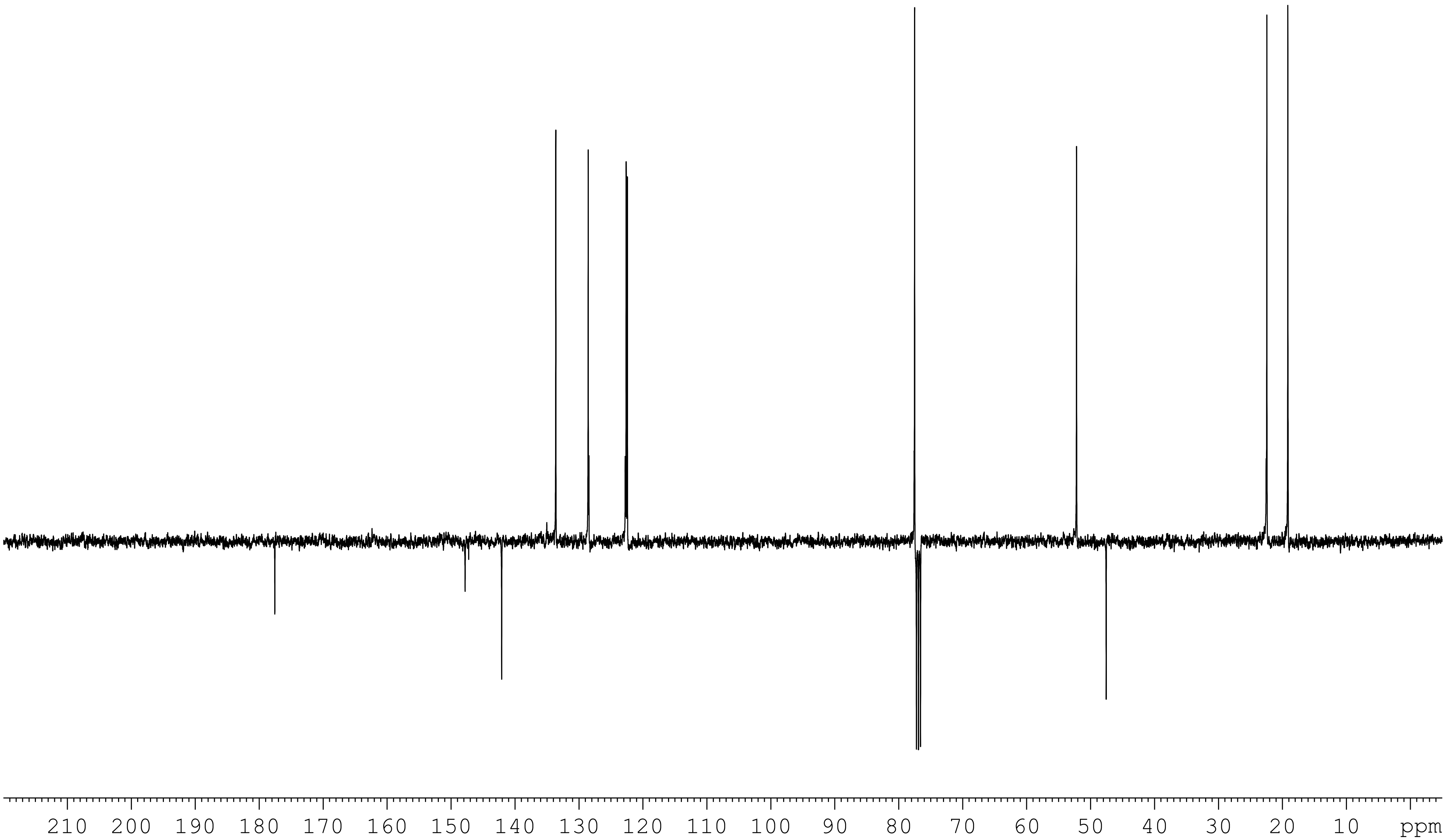
Methyl 3-(2’-chloro-6’-fluorophenyl)-3-hydroxy-2,2-dimethylpropanoate (3j)



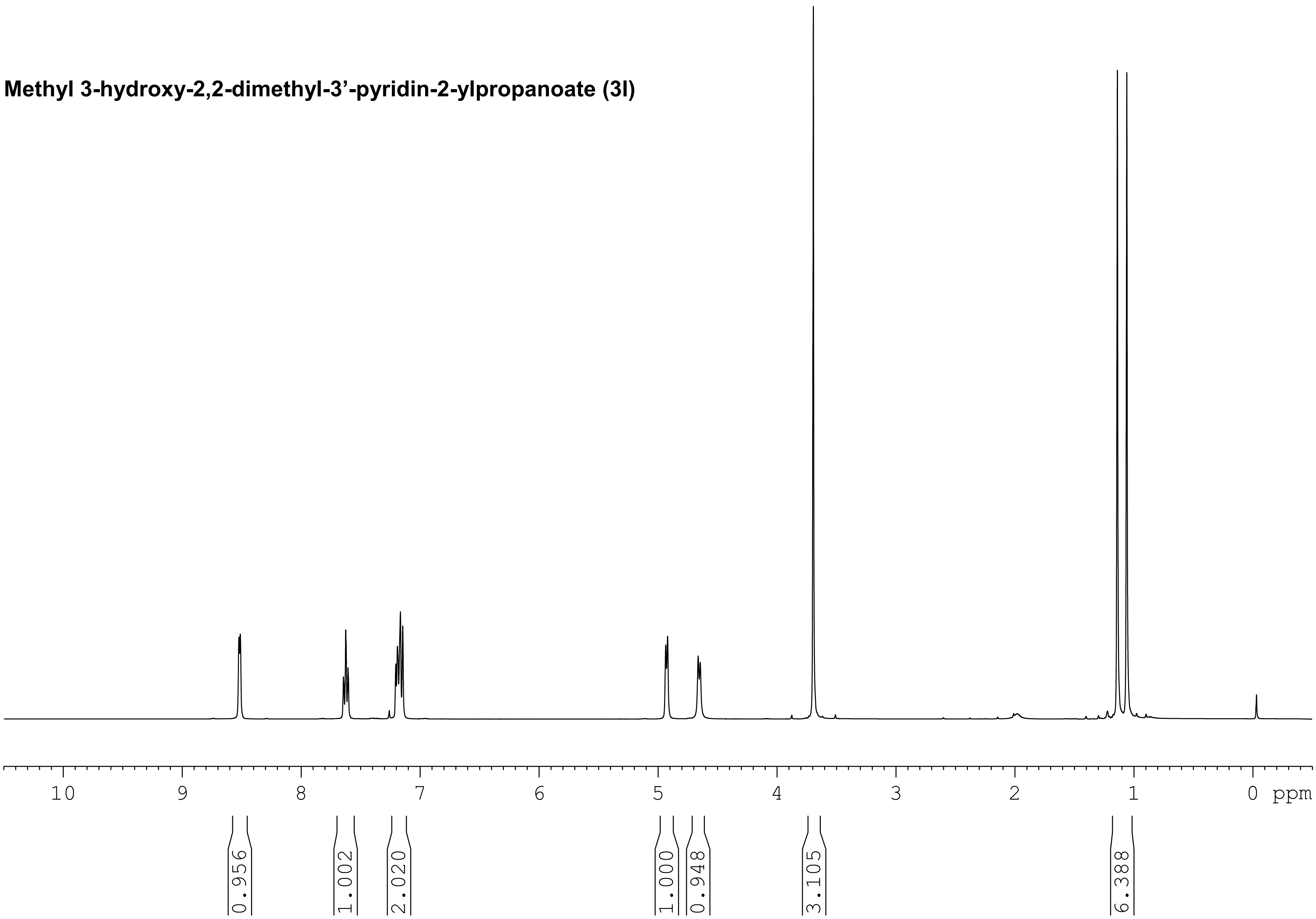
Methyl 3-hydroxy-2,2-dimethyl-3-(3’-nitrophenyl)propanoate (3k)



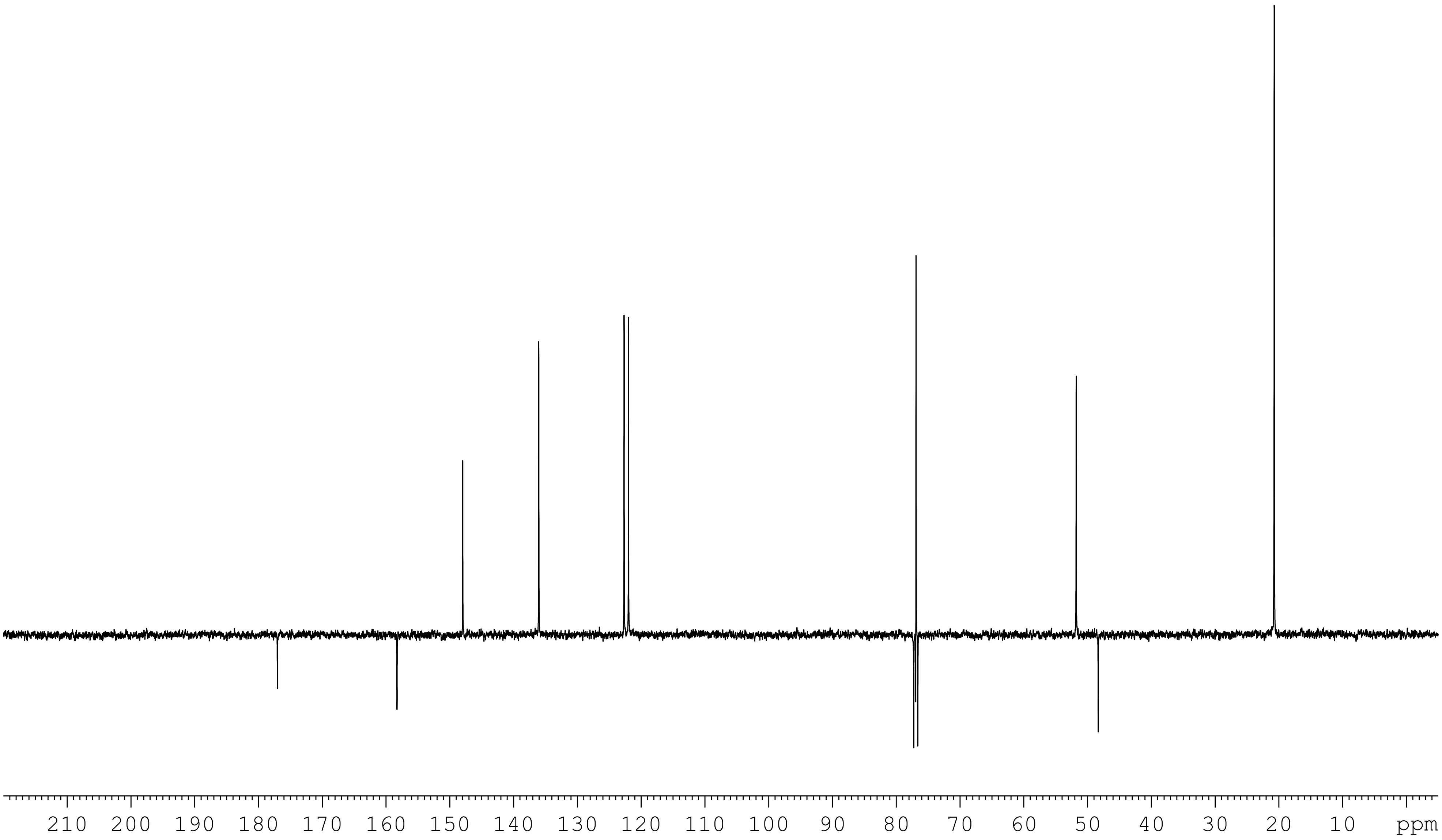
Methyl 3-hydroxy-2,2-dimethyl-3-(3'-nitrophenyl)propanoate (3k)



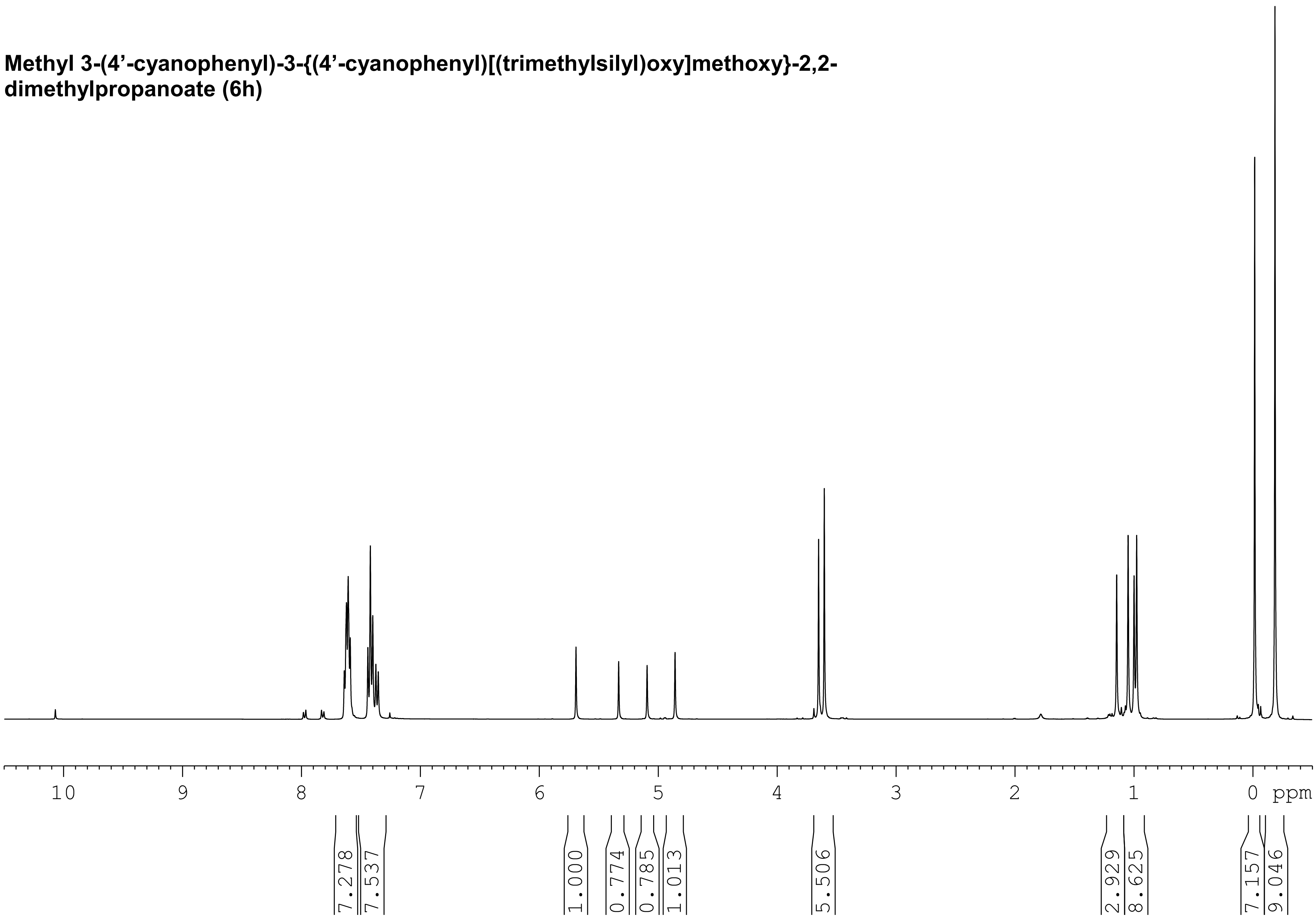
Methyl 3-hydroxy-2,2-dimethyl-3'-pyridin-2-ylpropanoate (3l)



Methyl 3-hydroxy-2,2-dimethyl-3'-pyridin-2-ylpropanoate (3l)



Methyl 3-(4’-cyanophenyl)-3-{(4’-cyanophenyl)[(trimethylsilyl)oxy]methoxy}-2,2-dimethylpropanoate (6h)



Methyl 3-(4’-cyanophenyl)-3-{(4’-cyanophenyl)[(trimethylsilyl)oxy]methoxy}-2,2-dimethylpropanoate (6h)