Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Total Synthesis of (−)-Cryptocaryol A

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Acquisition Time (sec)	3.1654	***Comment***	Paula PKK8 C6D6 250 MHz mar14pkkH1			***Date***	14 Mar 2013 18:54:14
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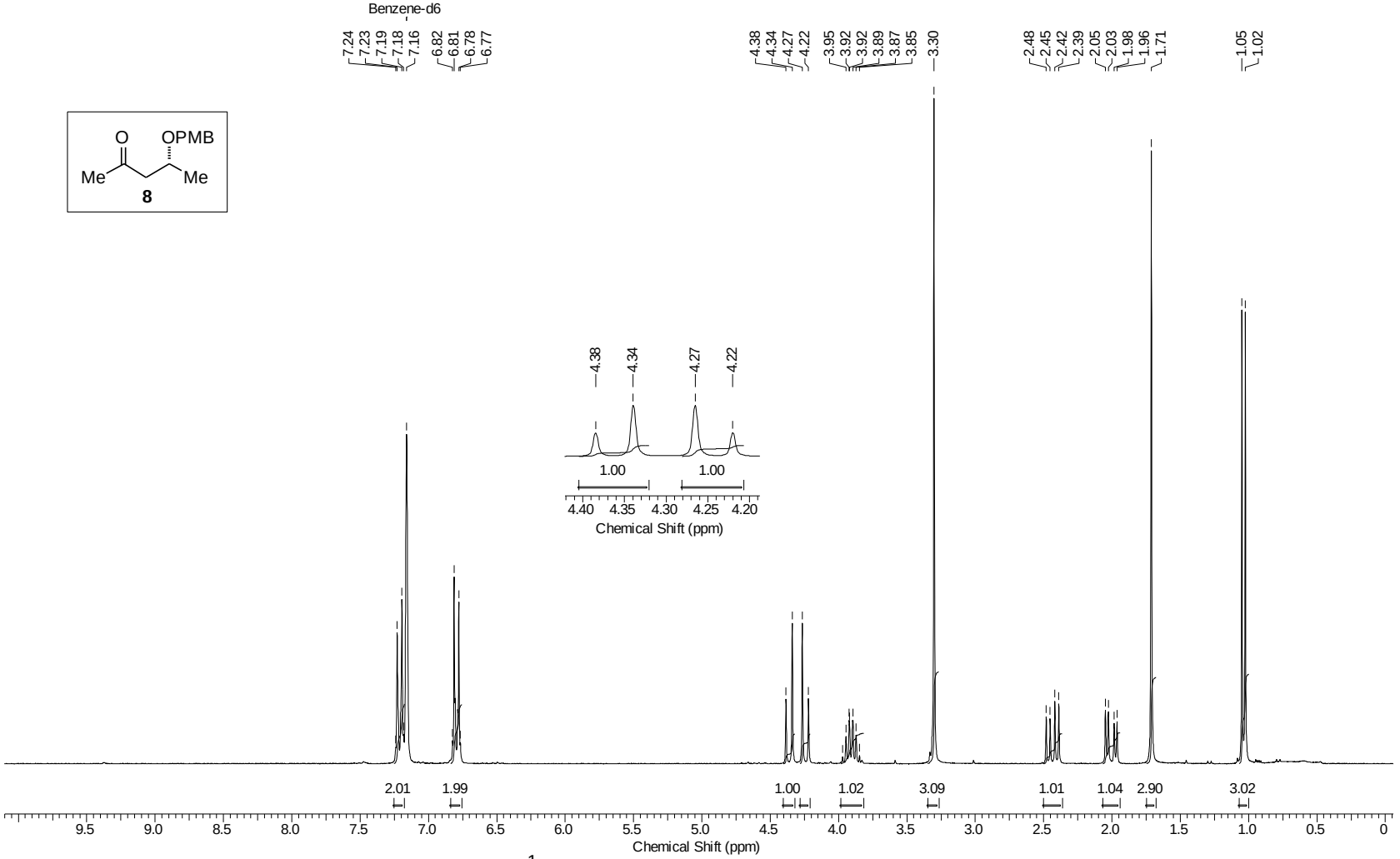

Figure S1. ^{1}H NMR spectrum of **8** (250 MHz; C_6D_6).

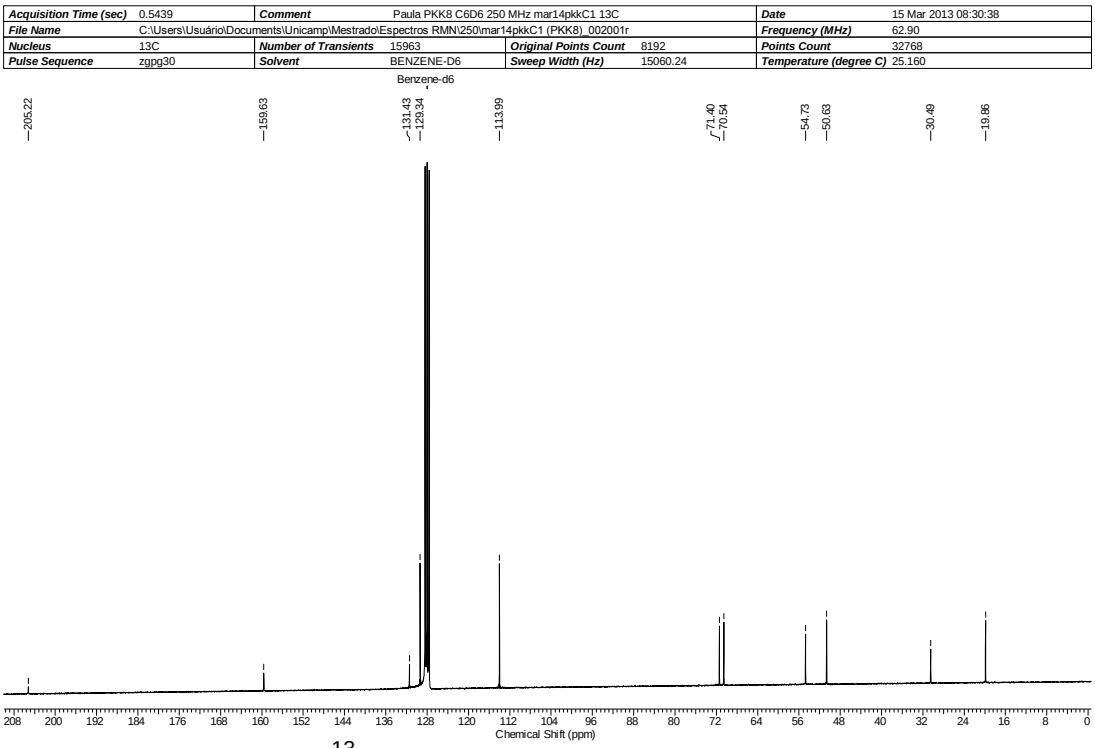

Figure S2. ^{13}C NMR spectrum of **8** (62.5 MHz; C_6D_6).

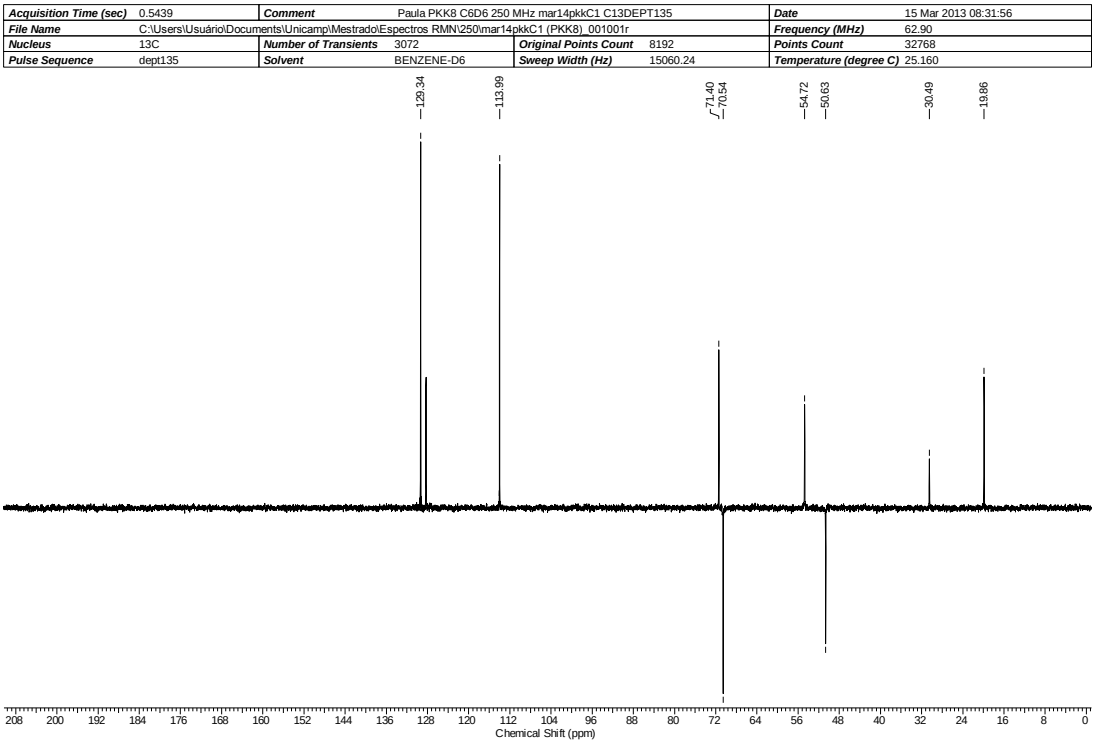

Figure S3. ^{13}C NMR spectrum (DEPT 135) of **8** (62.5 MHz; C_6D_6).

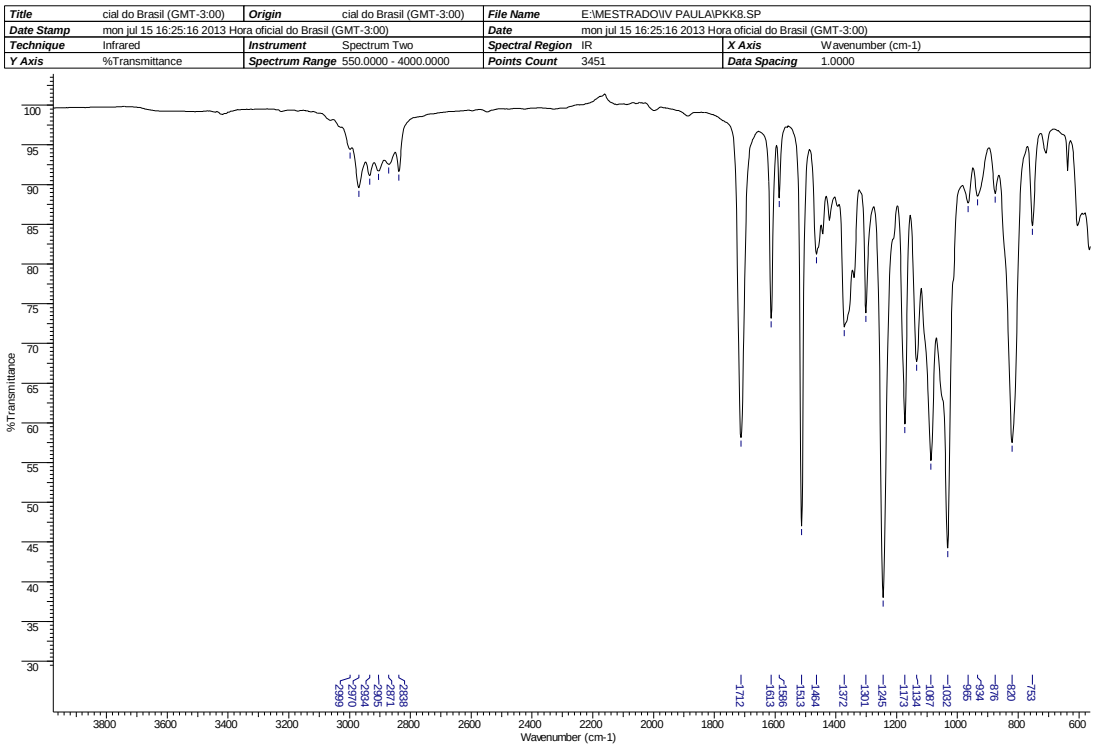

Figure S4. IR spectrum of **8**.

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Sweep Width (Hz)	12335.53	***Temperature (degree C)***	25.153						

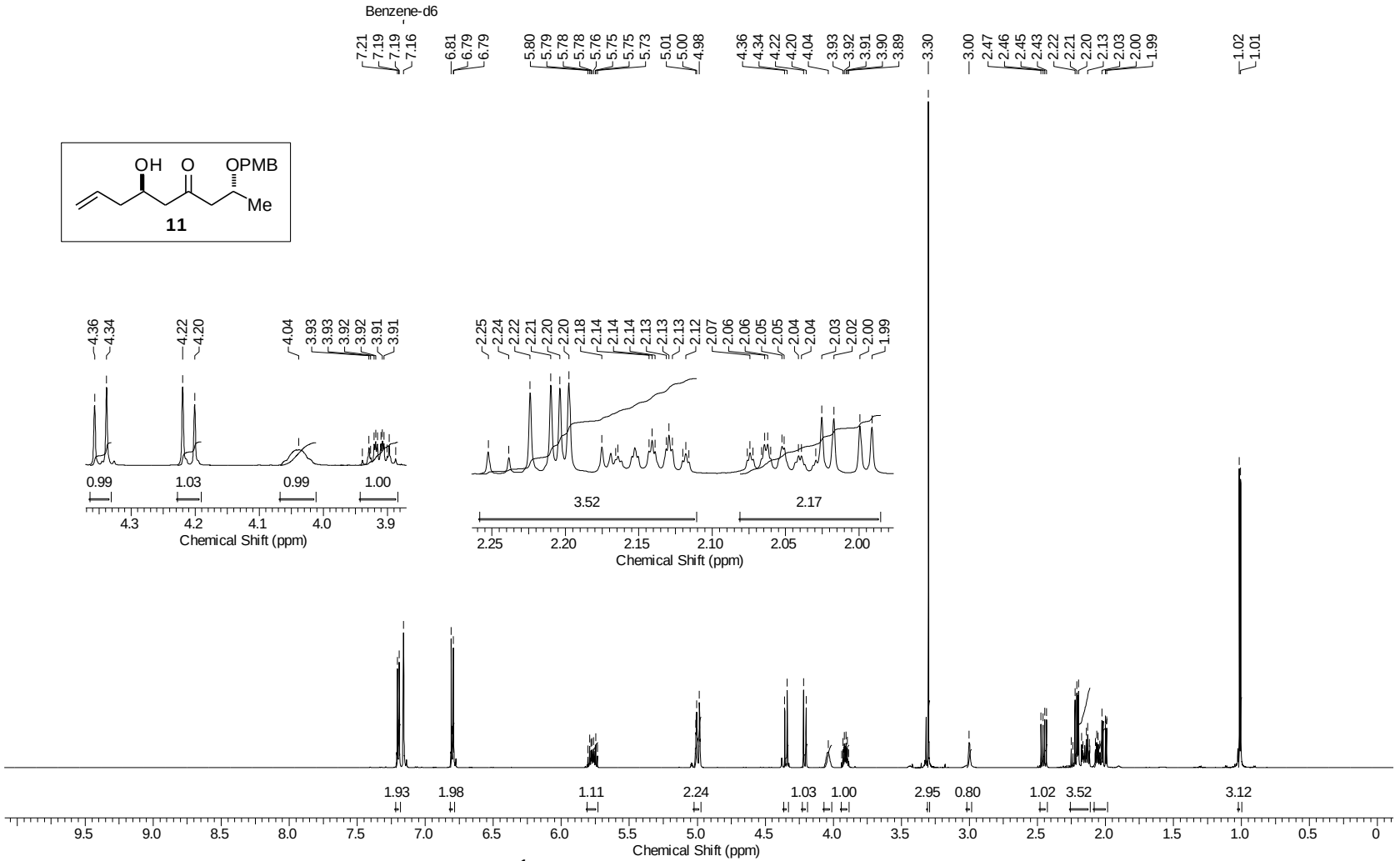


Figure S5. ^{1}H NMR spectrum of **11** (600 MHz; C_6D_6).

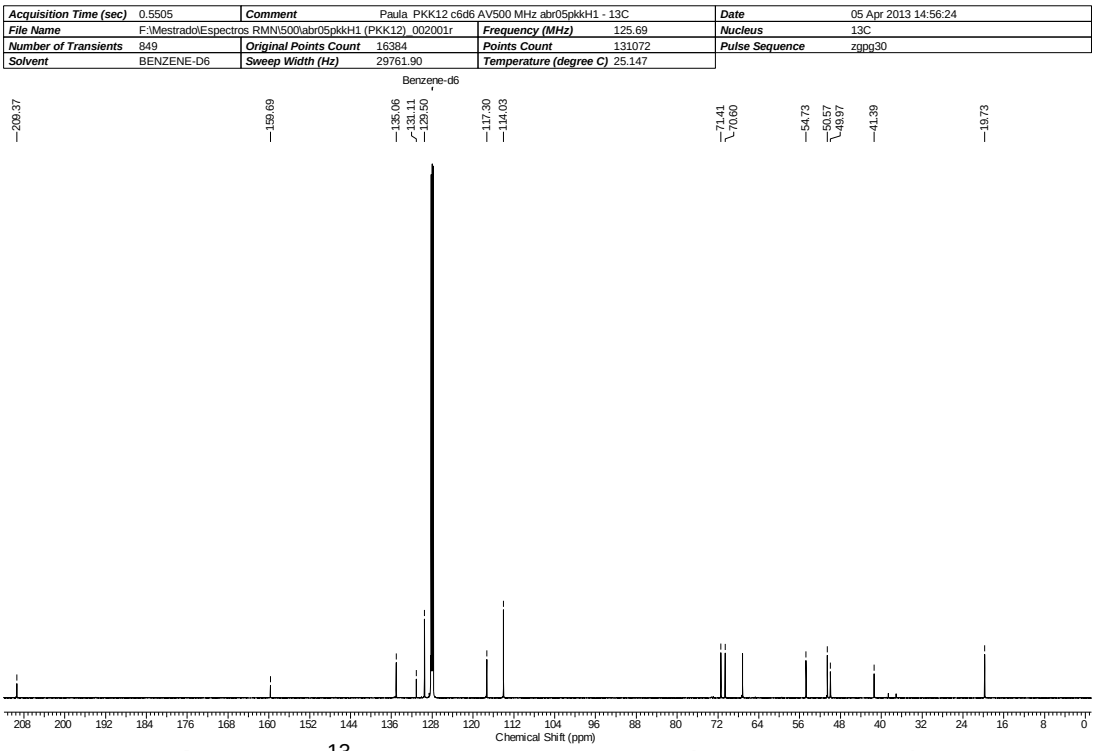


Figure S6. ^{13}C NMR spectrum of **11** (125 MHz; C_6D_6).

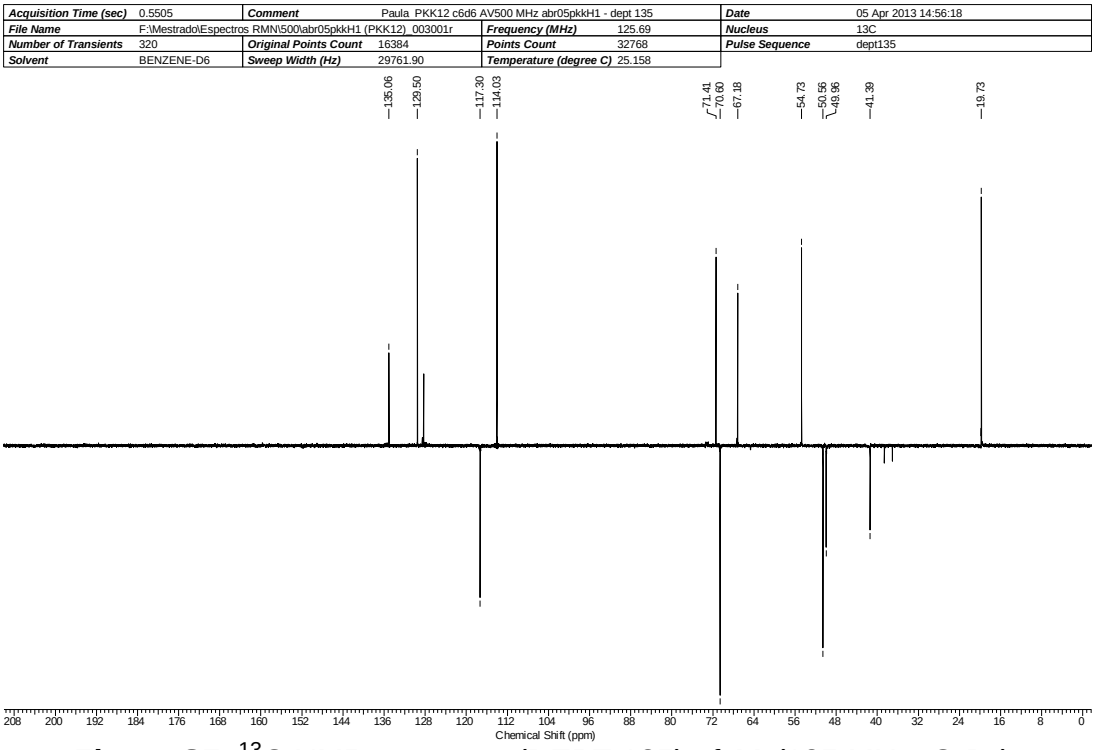
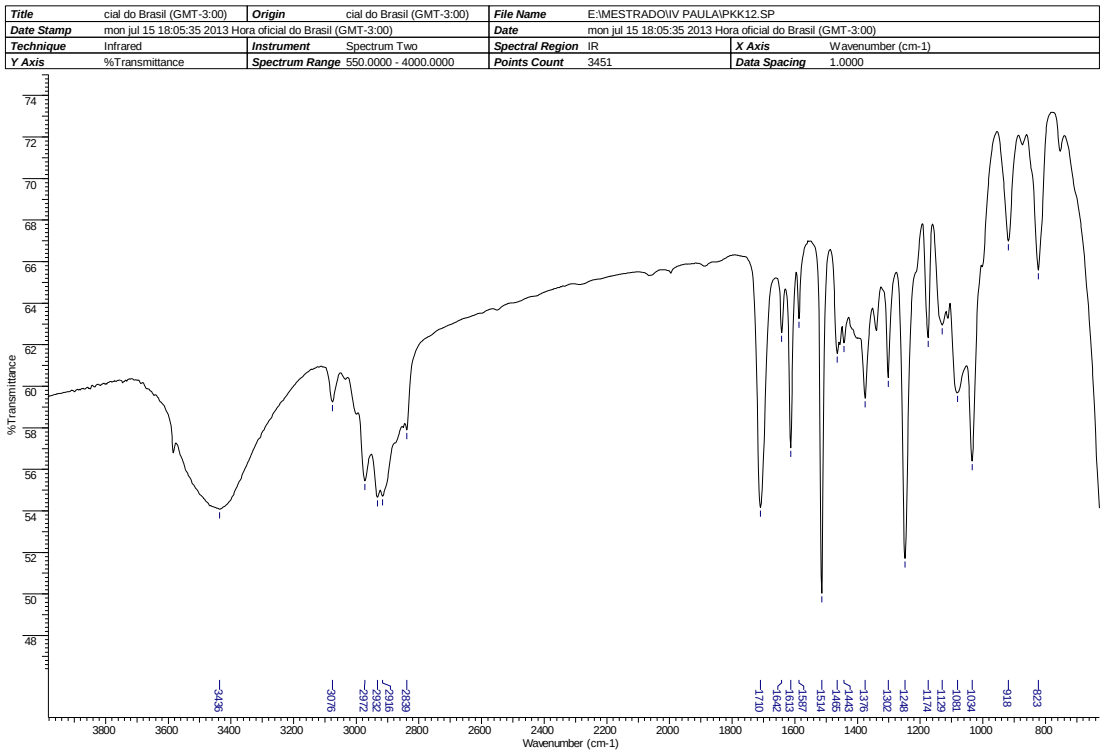


Figure S7. ^{13}C NMR spectrum (DEPT 135) of **11** (125 MHz; C_6D_6).



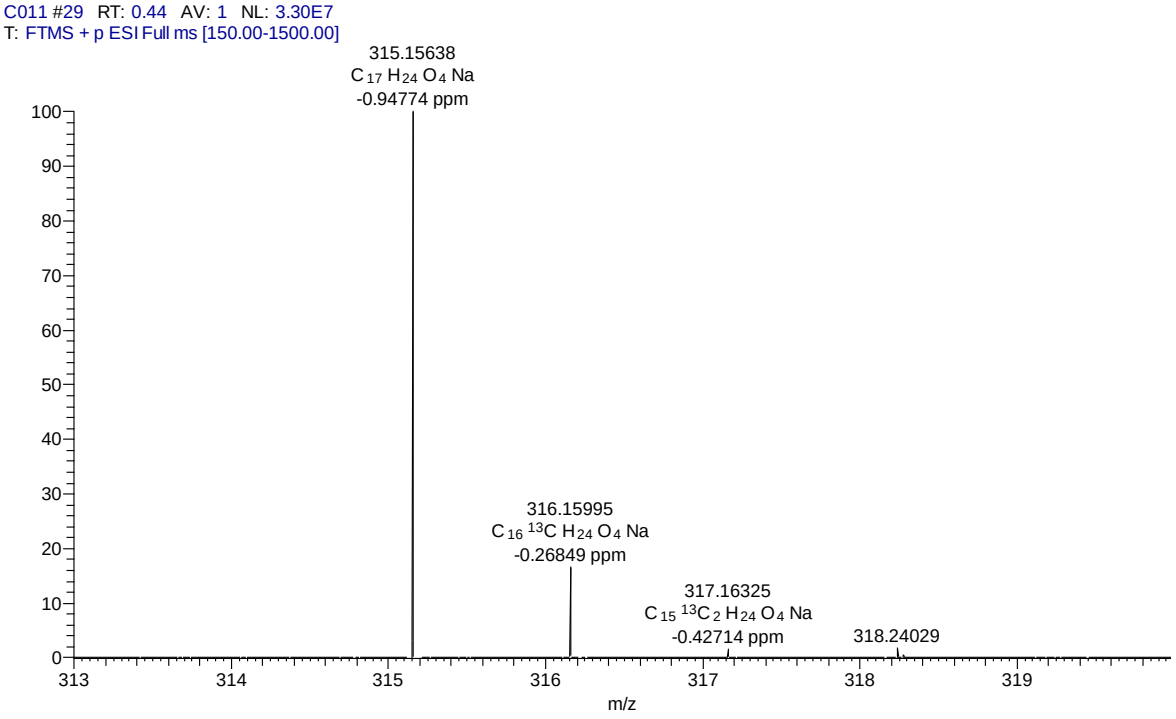


Figure S8. IR and HRMS spectra of **11**.

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Solvent	CHLOROFORM-D			***Sweep Width (Hz)***	10000.00	***Temperature (degree C)***	25.136

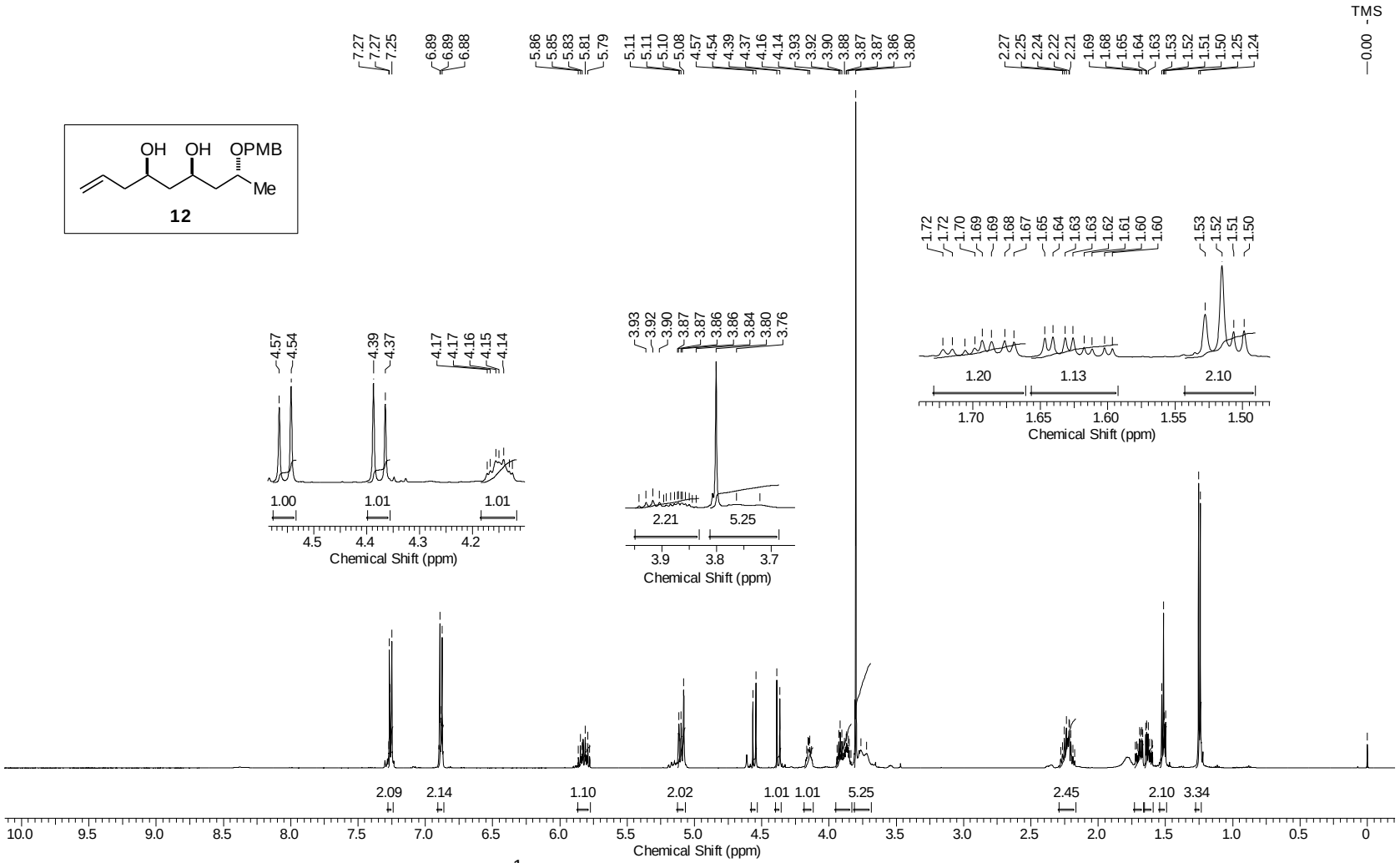


Figure S9. ^{1}H NMR spectrum of **12** (500 MHz; $CDCl_3$).

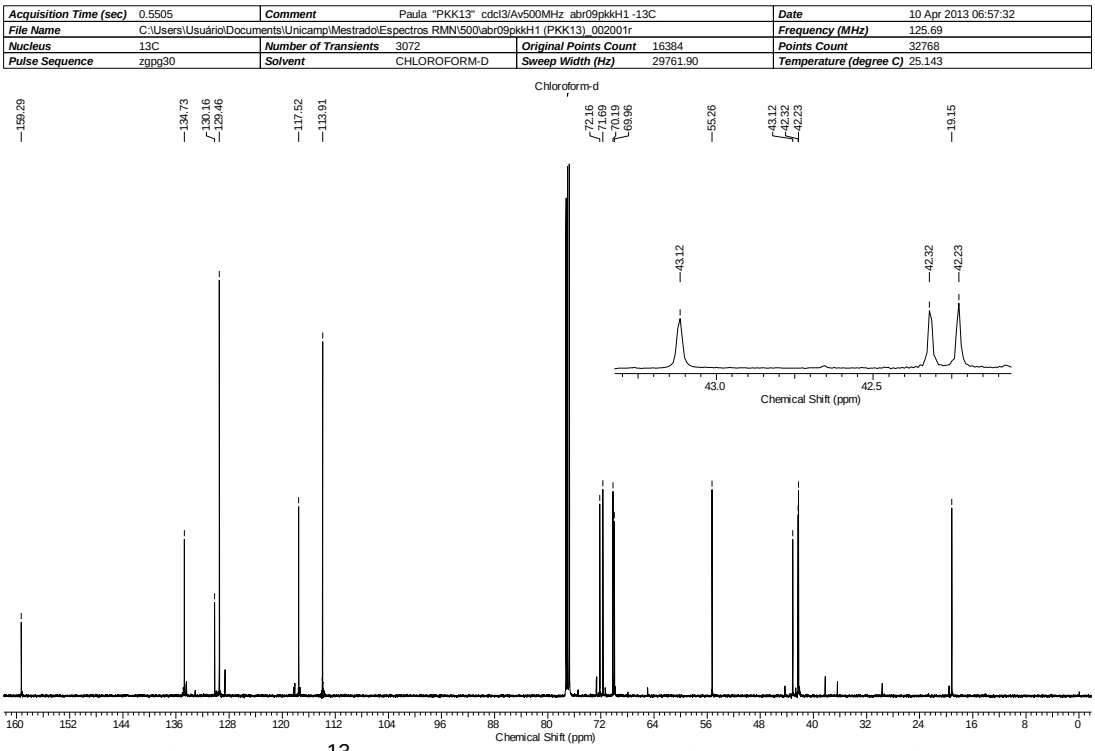


Figure S10. ^{13}C NMR spectrum of **12** (125 MHz; $CDCl_3$).

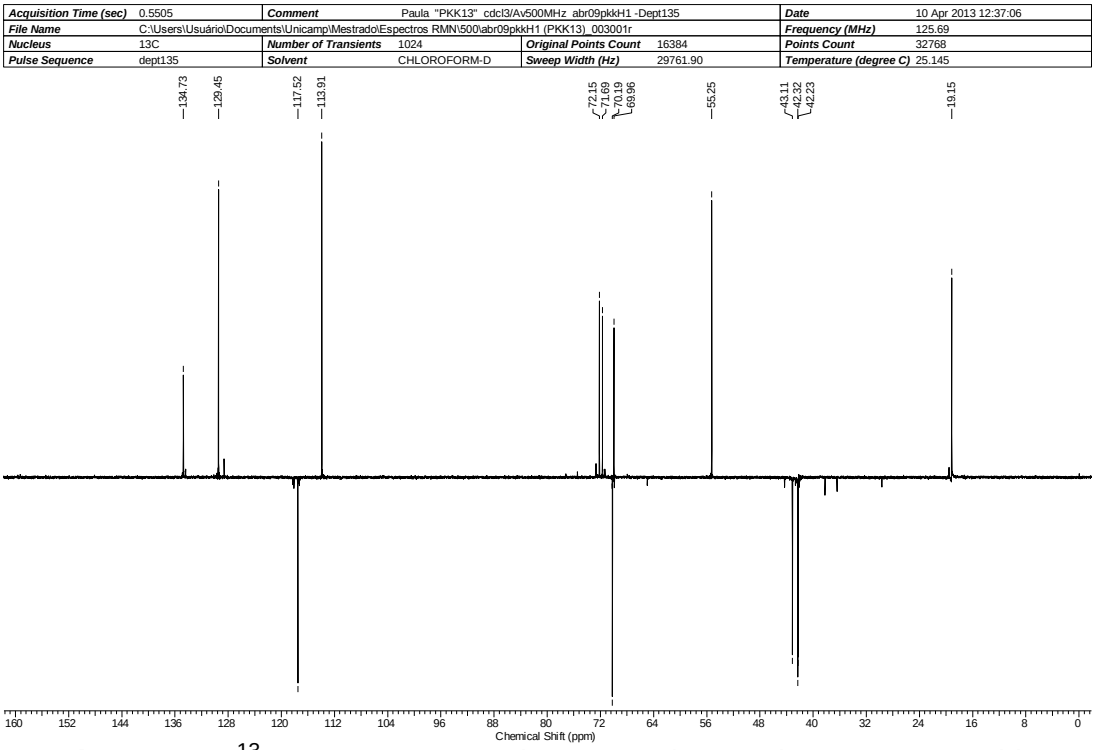
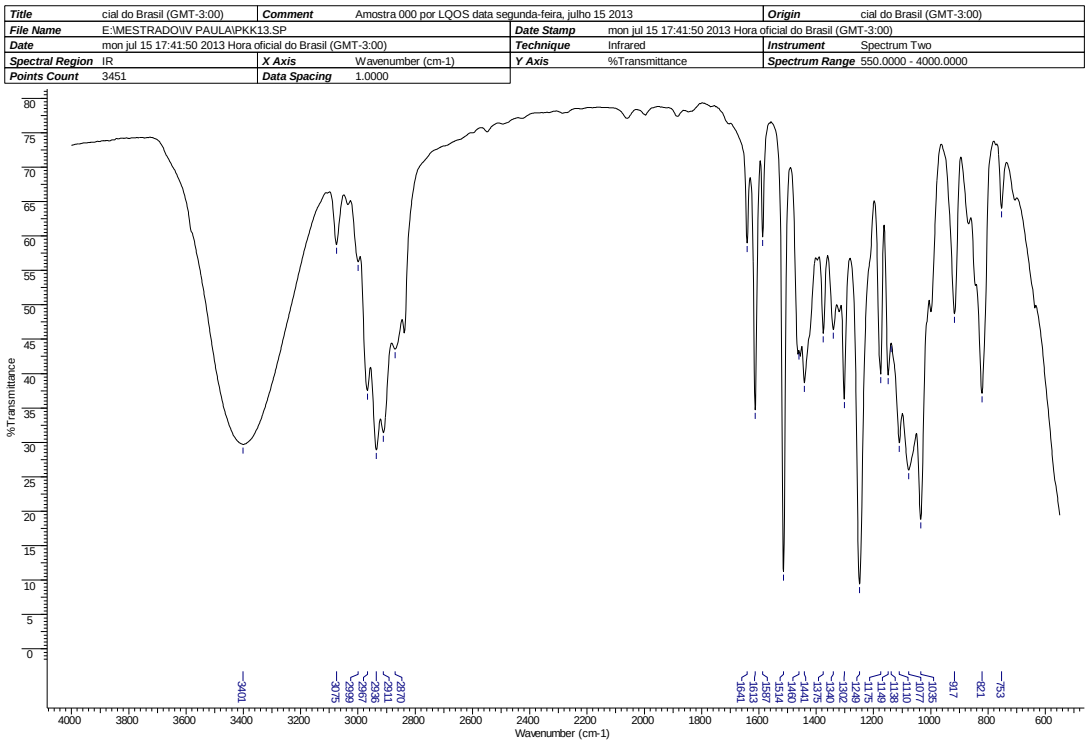


Figure S11. ^{13}C NMR spectrum (DEPT 135) of **12** (125 MHz; $CDCl_3$).



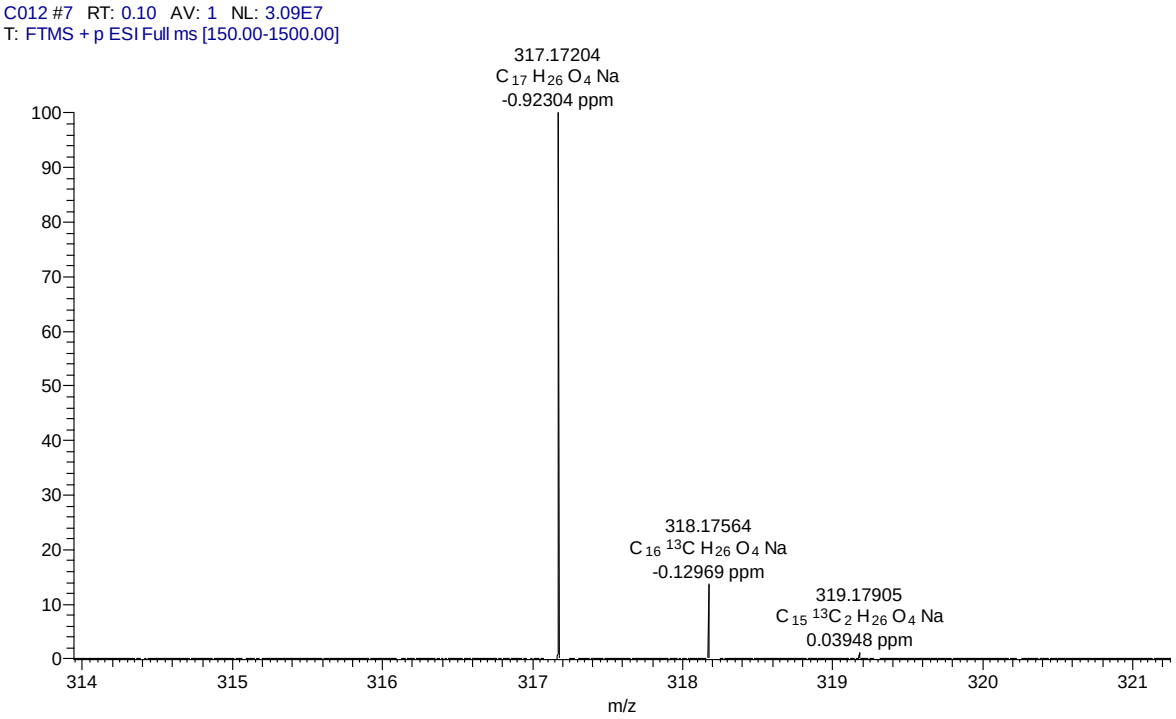


Figure S12. IR and HRMS spectra of **12**.

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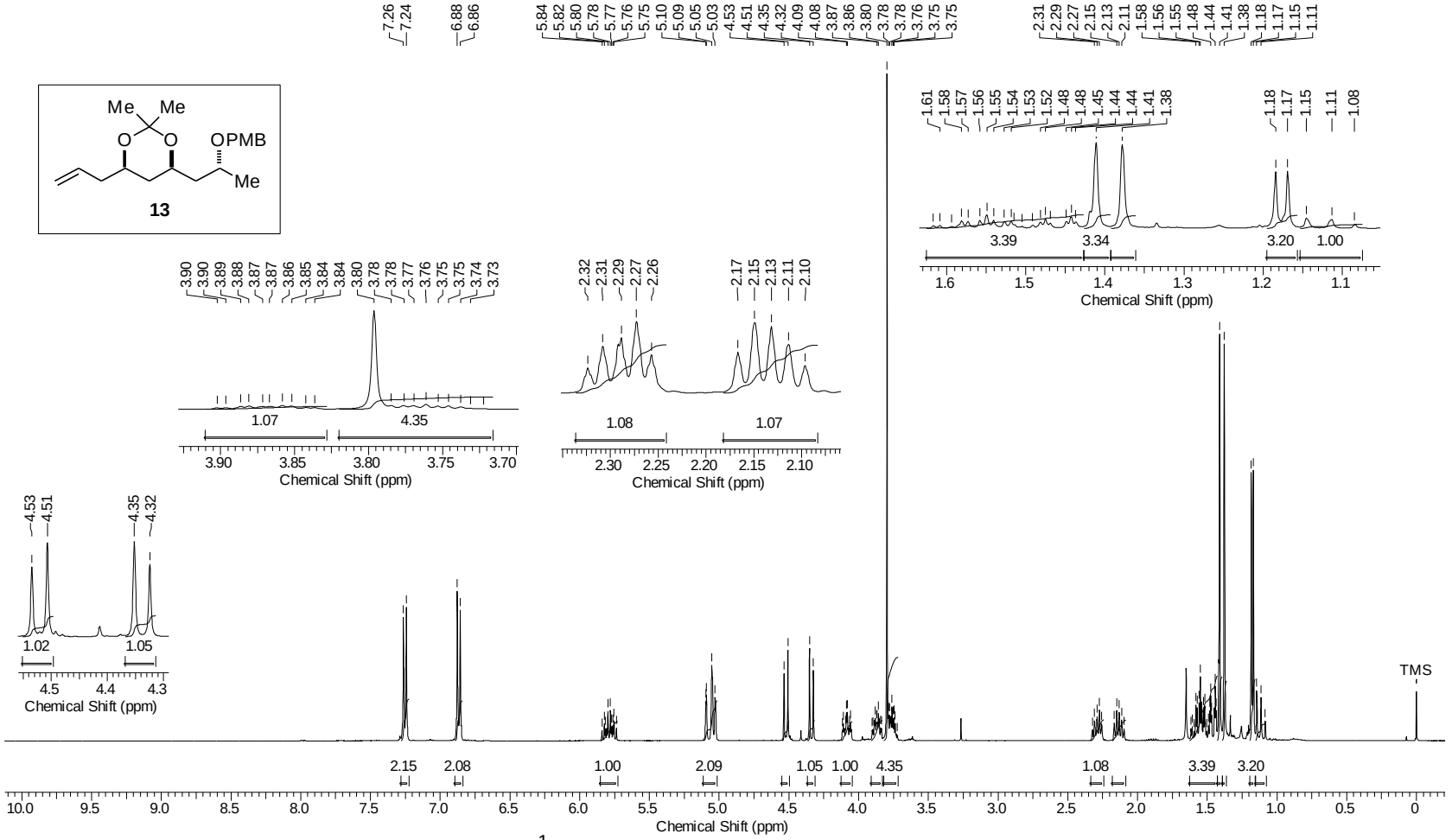


Figure S13. ^{1}H NMR spectrum of **13** (400 MHz; $CDCl_3$).

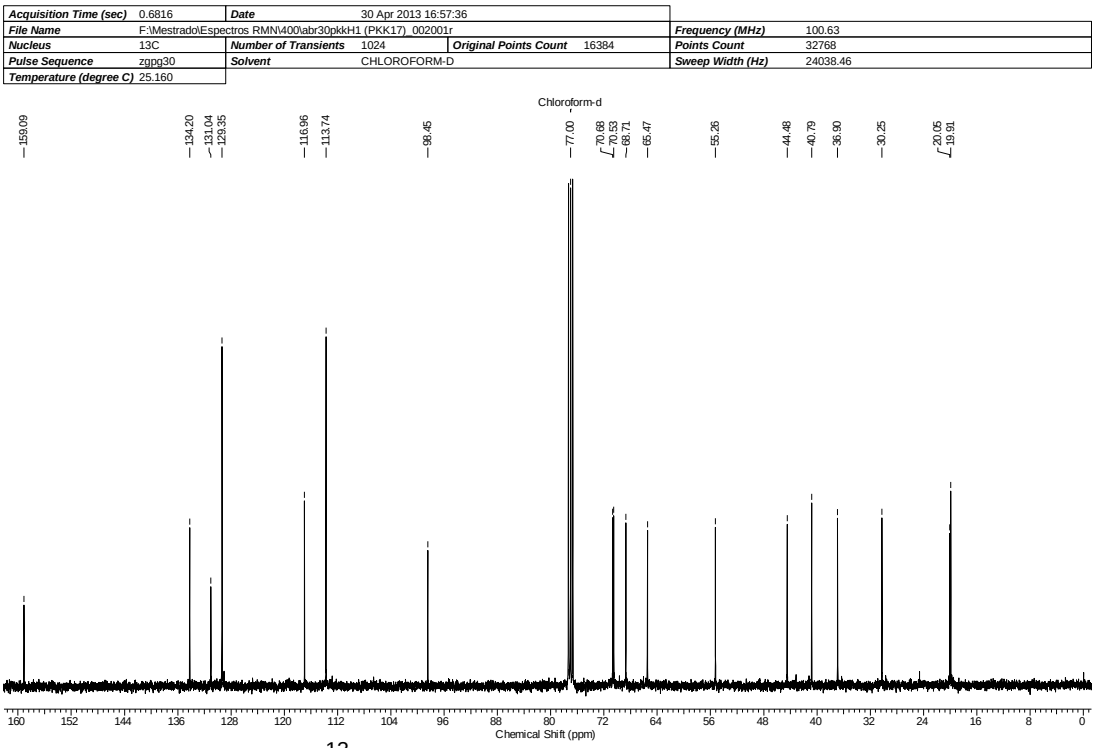


Figure S14. ^{13}C NMR spectrum of **13** (100 MHz; $CDCl_3$).

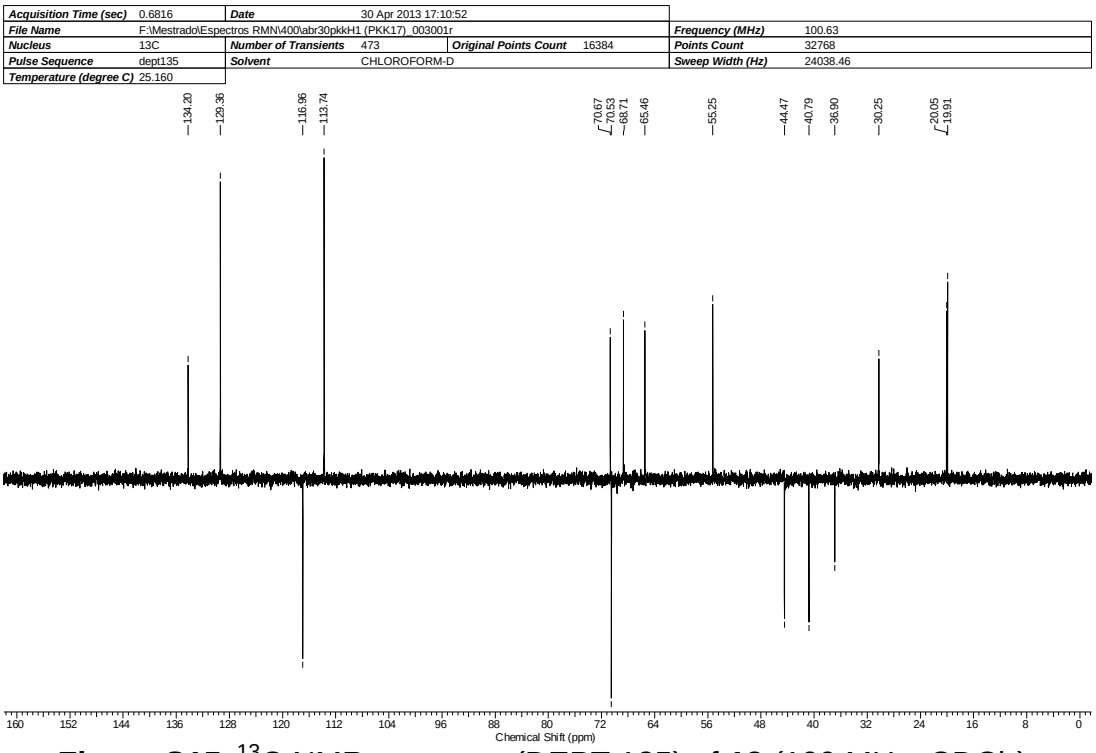
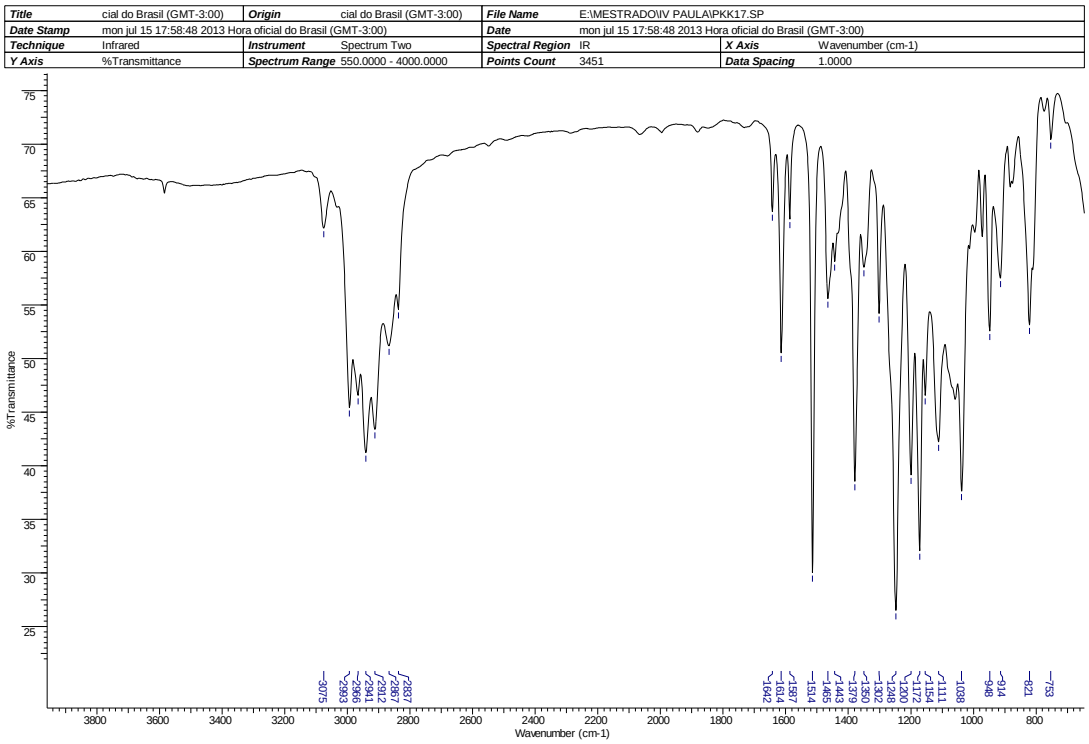


Figure S15. ^{13}C NMR spectrum (DEPT 135) of **13** (100 MHz; $CDCl_3$).



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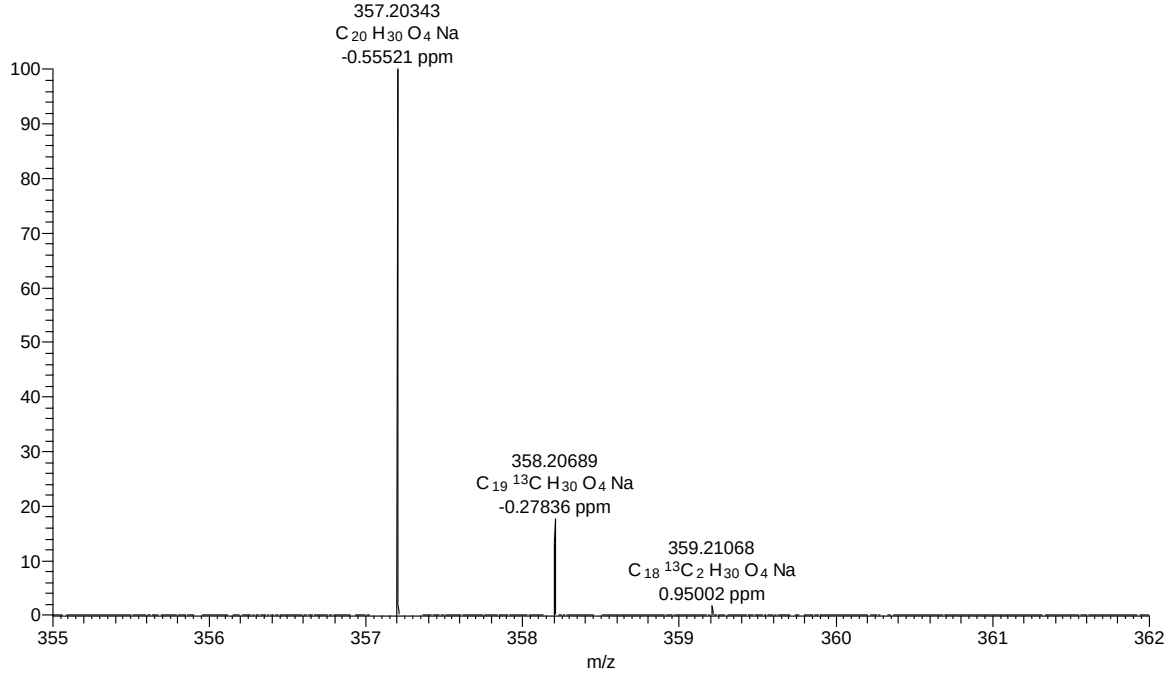

Figure S16. IR and HRMS spectra of **13**.

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File Name	F:\Mestrado\Espectros RMN\500\abr12pkkH2 (PKK16)_001001r			***Frequency (MHz)***	499.87	***Nucleus***	1H
Number of Transients	16	***Original Points Count***	16384	***Points Count***	65536	***Pulse Sequence***	zg30
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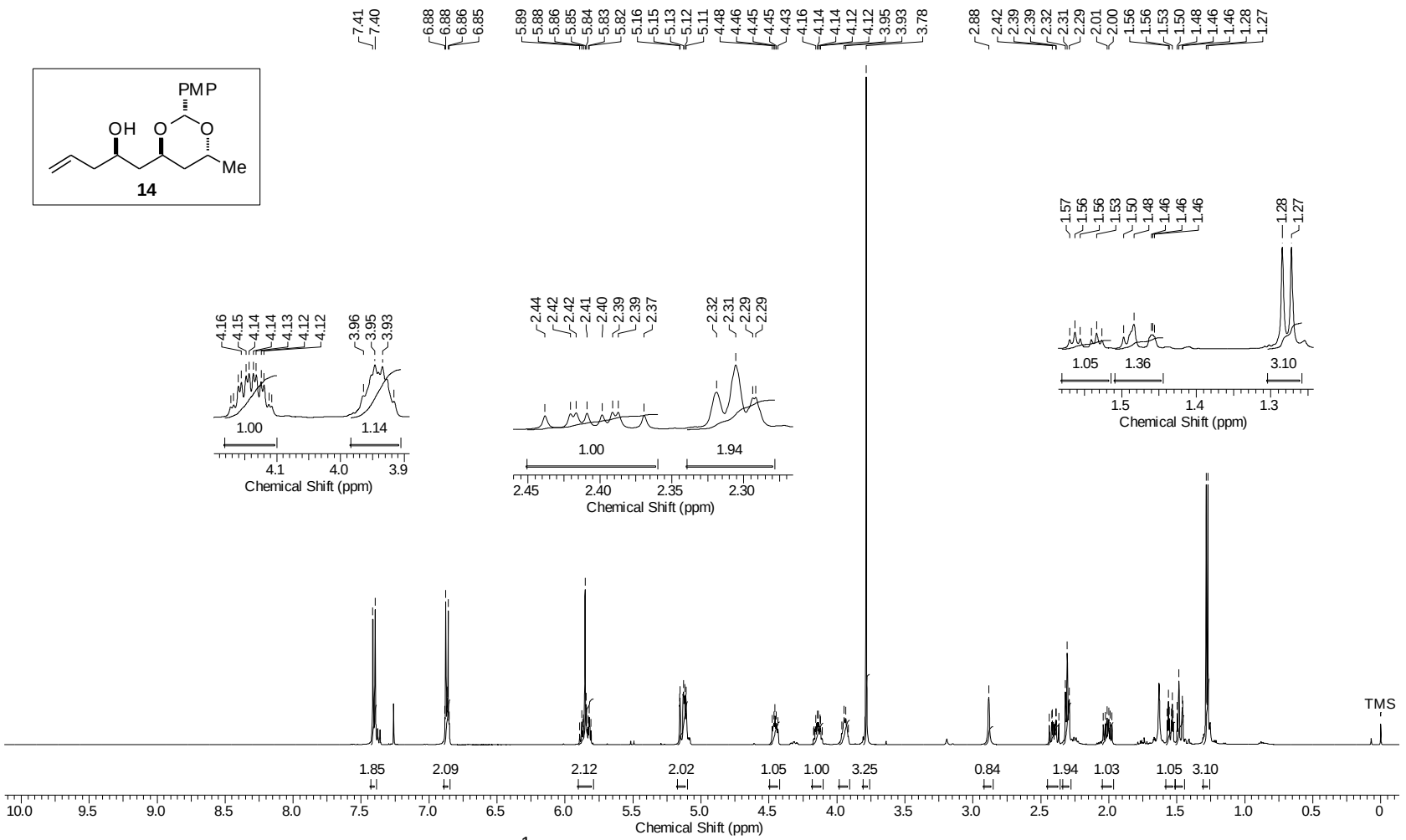

Figure S17. ^{1}H NMR spectrum of **14** (500 MHz; $CDCl_3$).

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Number of Transients	512	***Original Points Count***	16384	***Points Count***	32768	***Pulse Sequence***	zgpg30
Solvent	CHLOROFORM-D	***Sweep Width (Hz)***	29761.90	***Temperature (degree C)***	25.175		

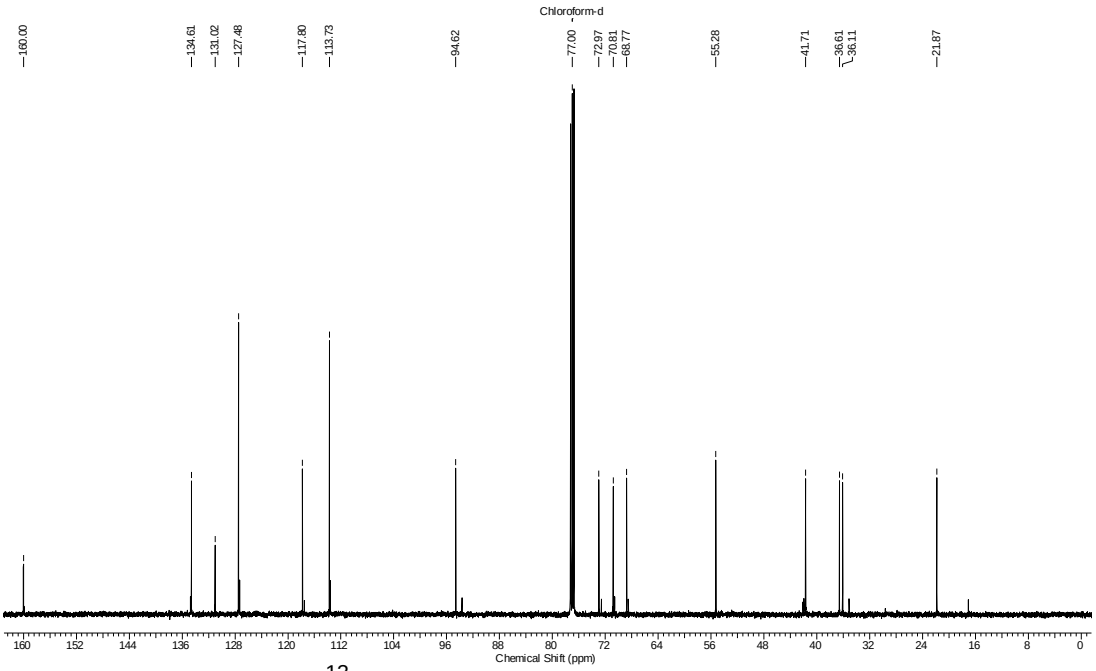

Figure S18. ^{13}C NMR spectrum of **14** (125 MHz; $CDCl_3$).

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Number of Transients	256	***Original Points Count***	16384	***Points Count***	32768	***Pulse Sequence***	dept135
Solvent	CHLOROFORM-D	***Sweep Width (Hz)***	29761.90	***Temperature (degree C)***	25.159		

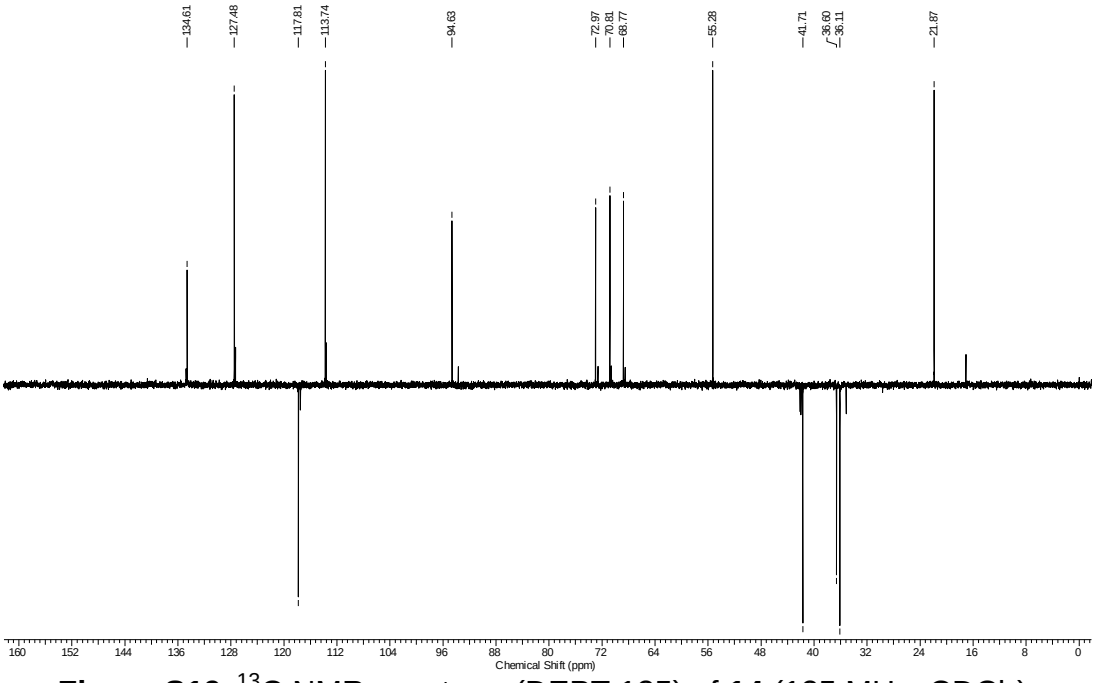


Figure S19. ^{13}C NMR spectrum (DEPT 135) of **14** (125 MHz; $CDCl_3$).

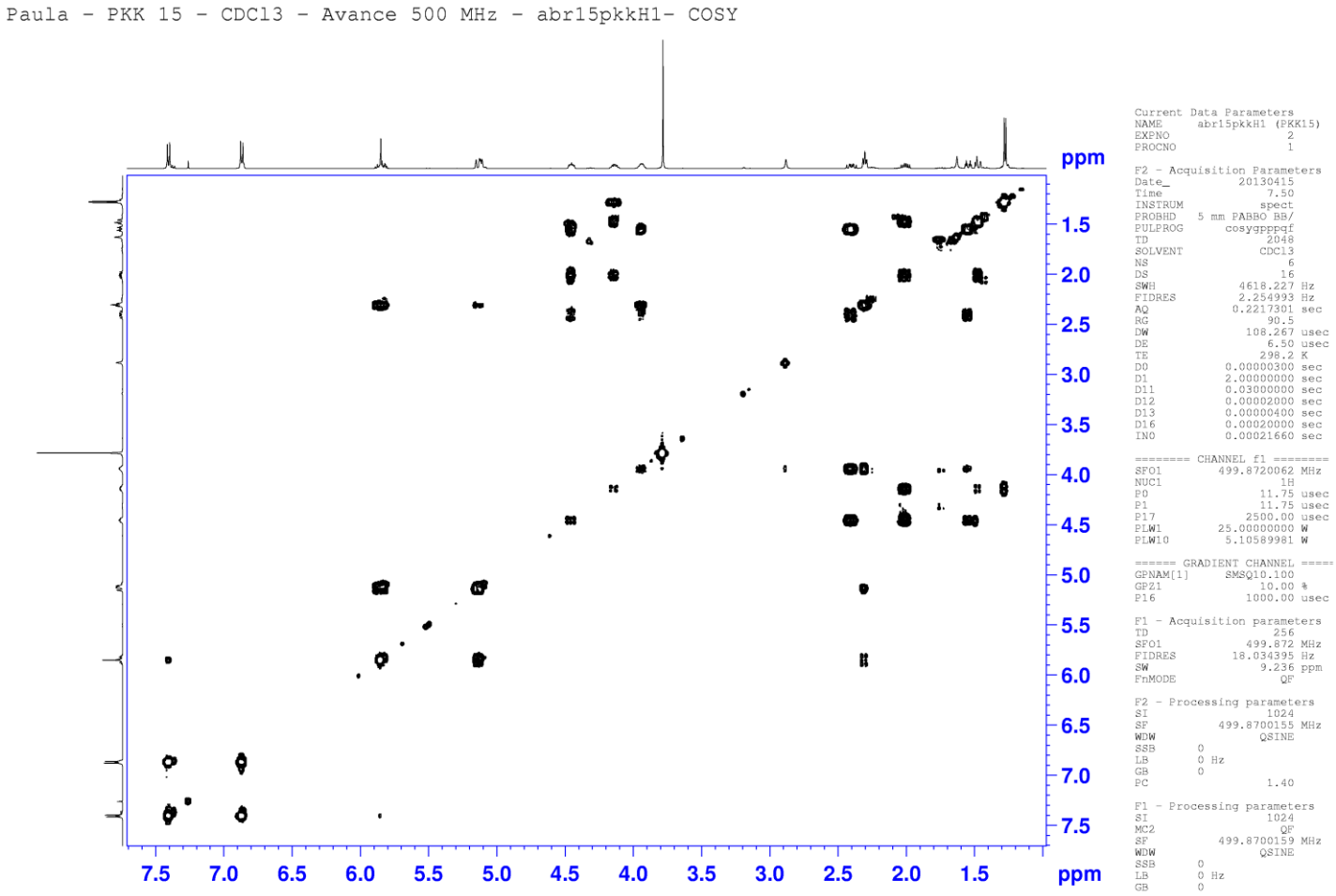


Figure S20. COSY contour map for **14**.

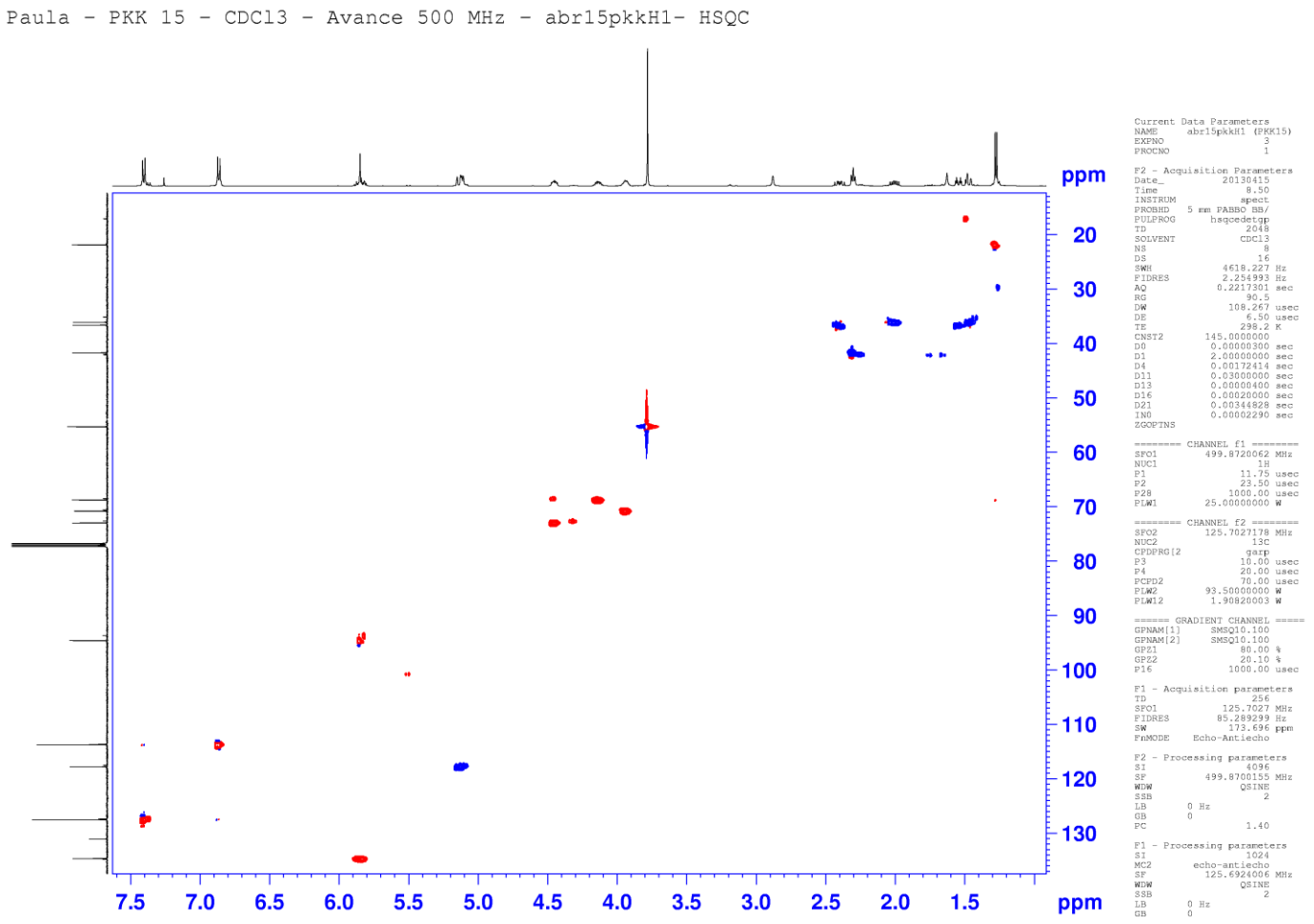


Figure S21. HSQC contour map for **14**.

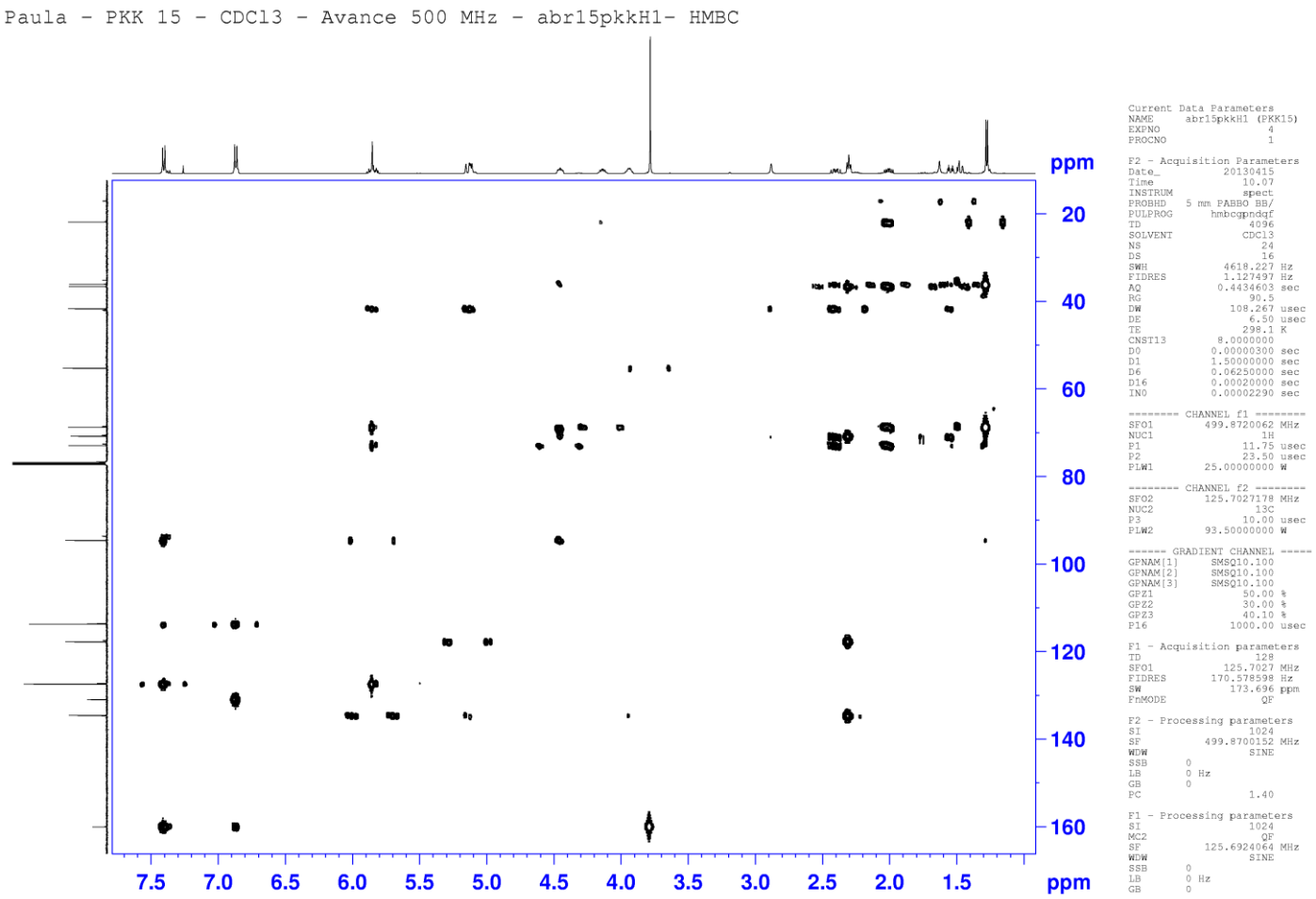
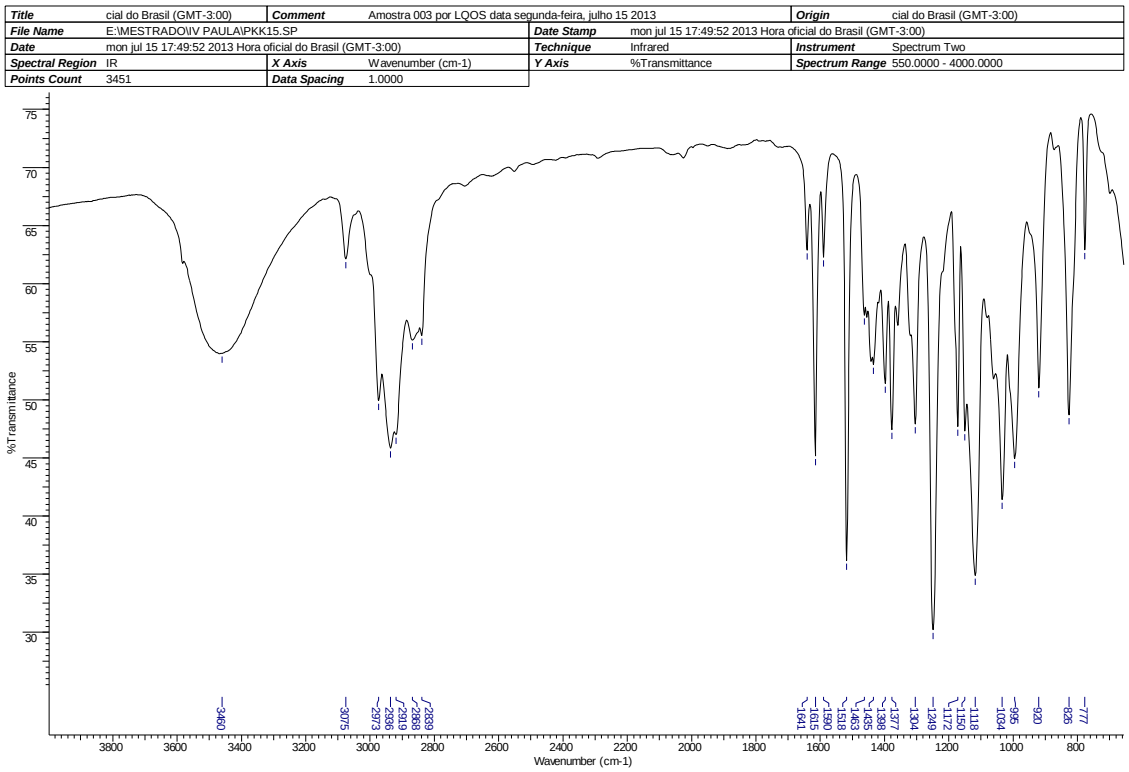


Figure S22. HMBC contour map for **14**.



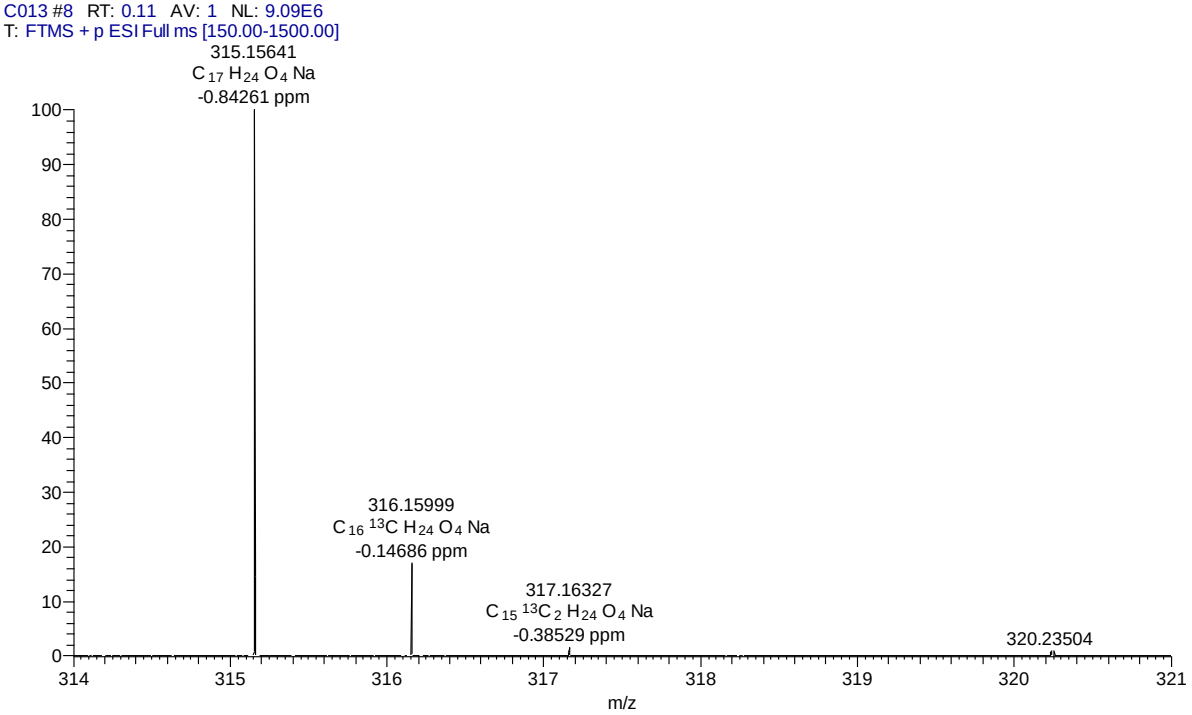


Figure S23. IR and HRMS spectra of **14**.

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Pulse Sequence	zg30	***Solvent***	CHLOROFORM-D			***Sweep Width (Hz)***	5175.98
Temperature (degree C)	25.160						

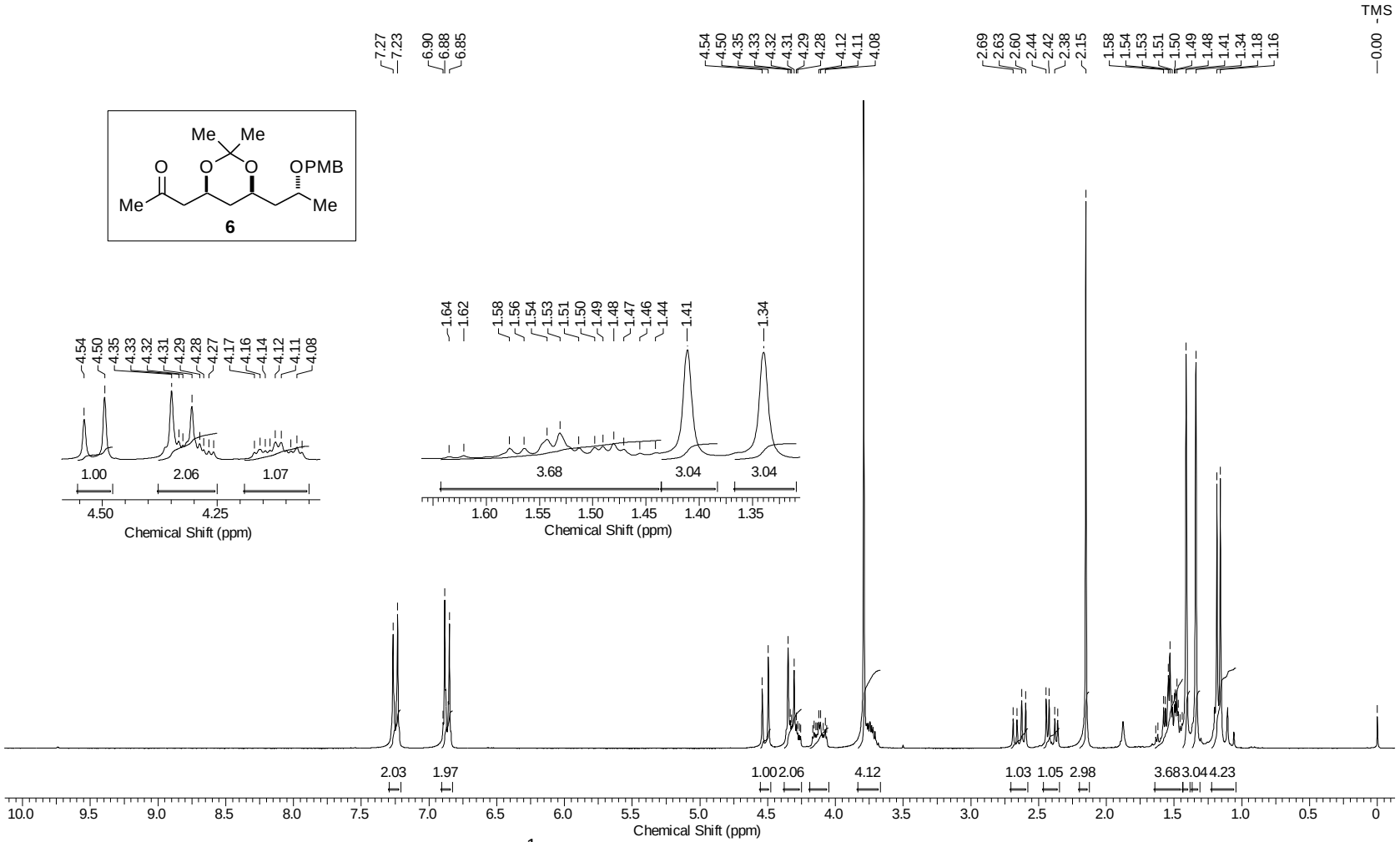

Figure S24. ^{1}H NMR spectrum of **6** (250 MHz; $CDCl_3$).

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Nucleus	13C	***Number of Transients***	10000	***Original Points Count***	8192	***Points Count***	32768
Pulse Sequence	zgpg30	***Solvent***	CHLOROFORM-D	***Sweep Width (Hz)***	15060.24	***Temperature (degree C)***	25.160

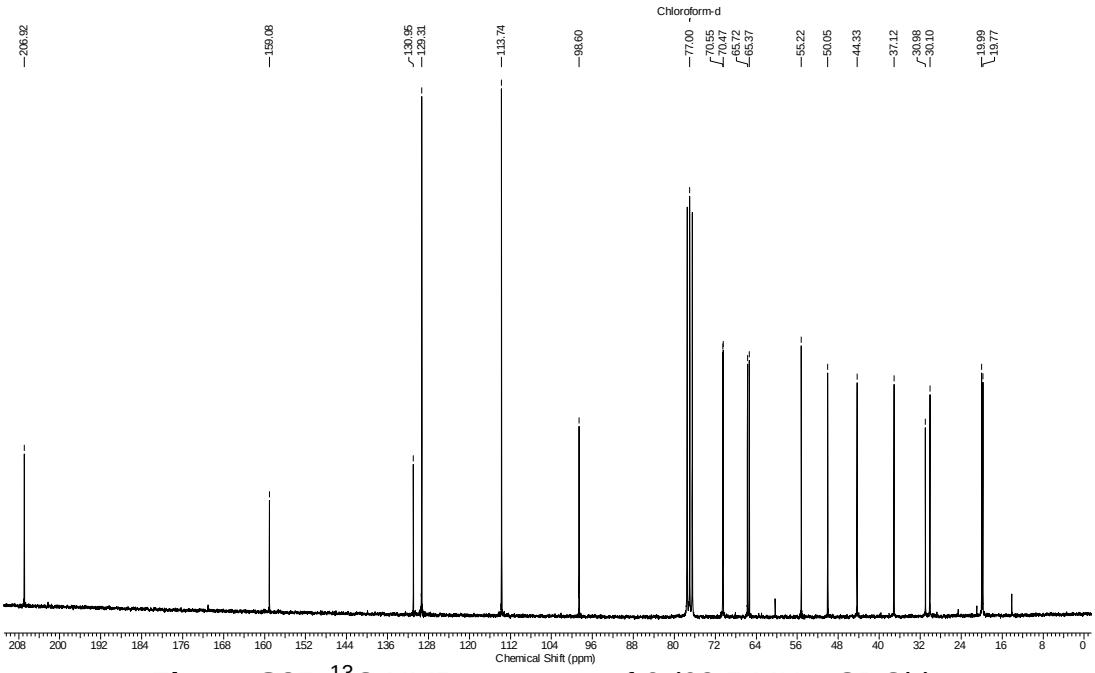

Figure S25. ^{13}C NMR spectrum of **6** (62.5 MHz; $CDCl_3$).

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Number of Transients	5000	***Original Points Count***	8192	***Points Count***	32768	***Pulse Sequence***	dept135
Solvent	CHLOROFORM-D			***Sweep Width (Hz)***	15060.24	***Temperature (degree C)***	25.160

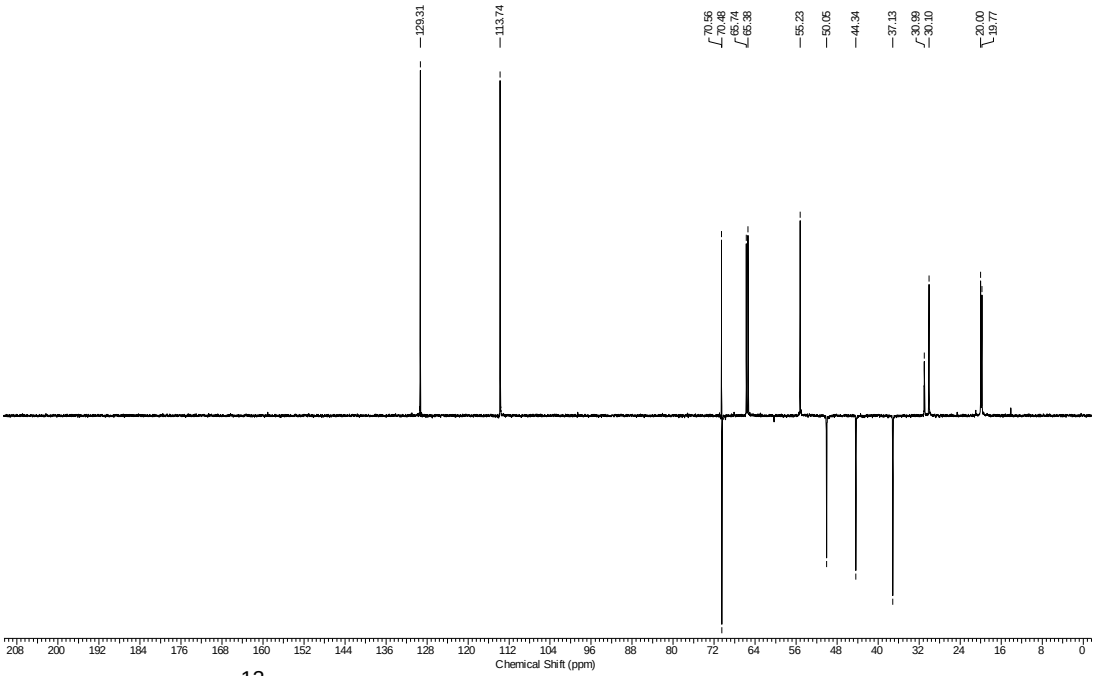
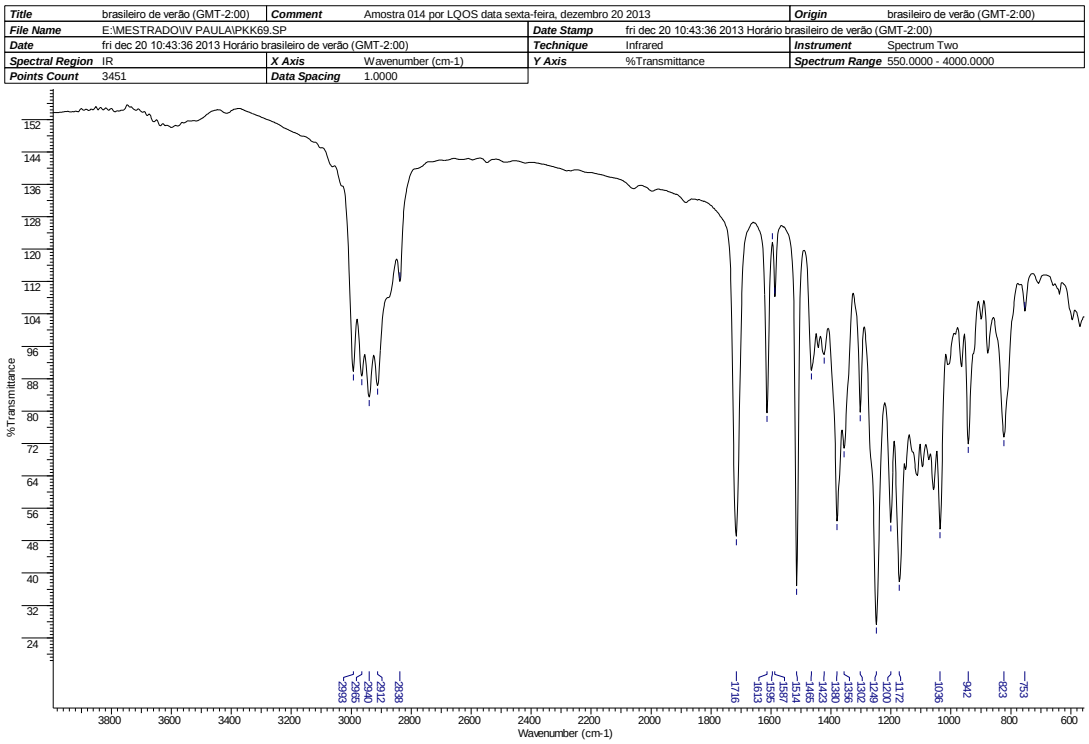


Figure S26. ^{13}C NMR spectrum (DEPT 135) of **6** (62.5 MHz; $CDCl_3$).



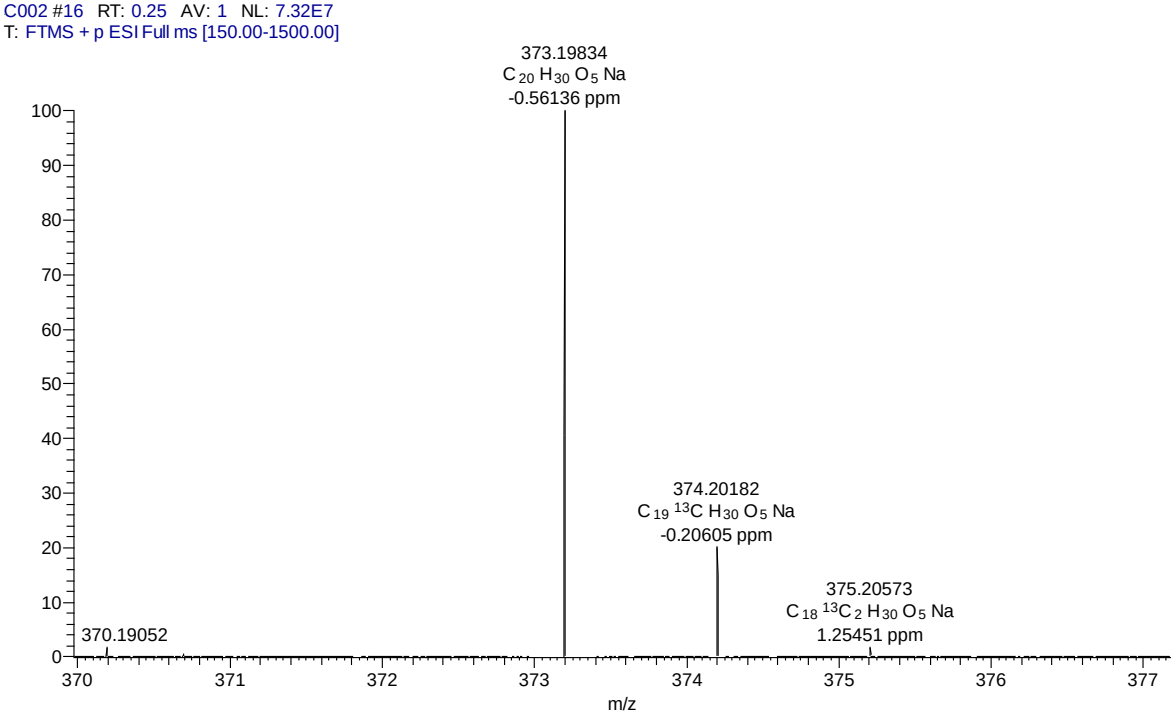


Figure S27. IR and HRMS spectra of **6**.

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Number of Transients	16	***Original Points Count***	16384	***Points Count***	65536	***Pulse Sequence***	zg30
Solvent	BENZENE-D6	***Sweep Width (Hz)***	10000.00	***Temperature (degree C)***	25.154		

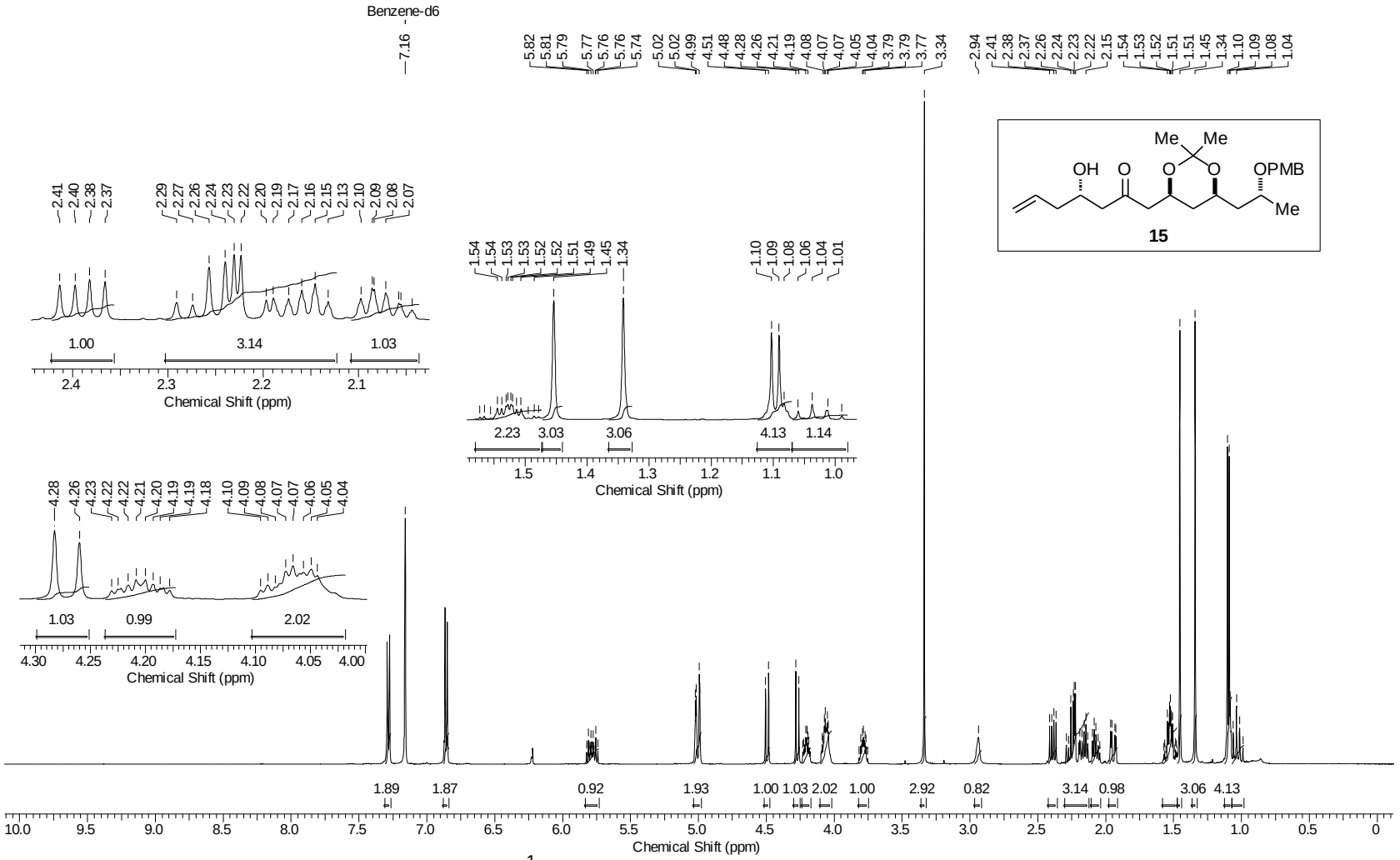


Figure S28. ^{1}H NMR spectrum of **15** (500 MHz; C_6D_6).

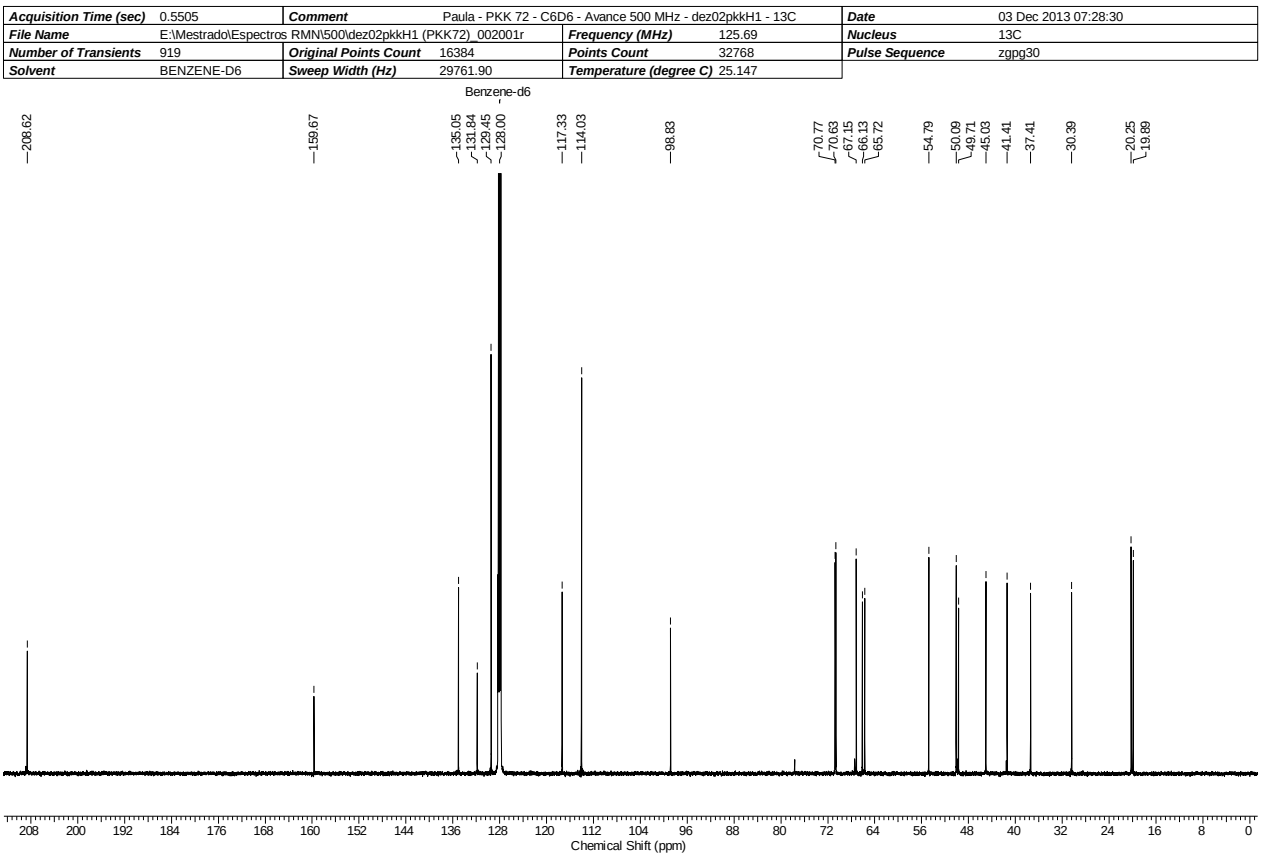


Figure S29. ^{13}C NMR spectrum of **15** (125 MHz; C_6D_6).

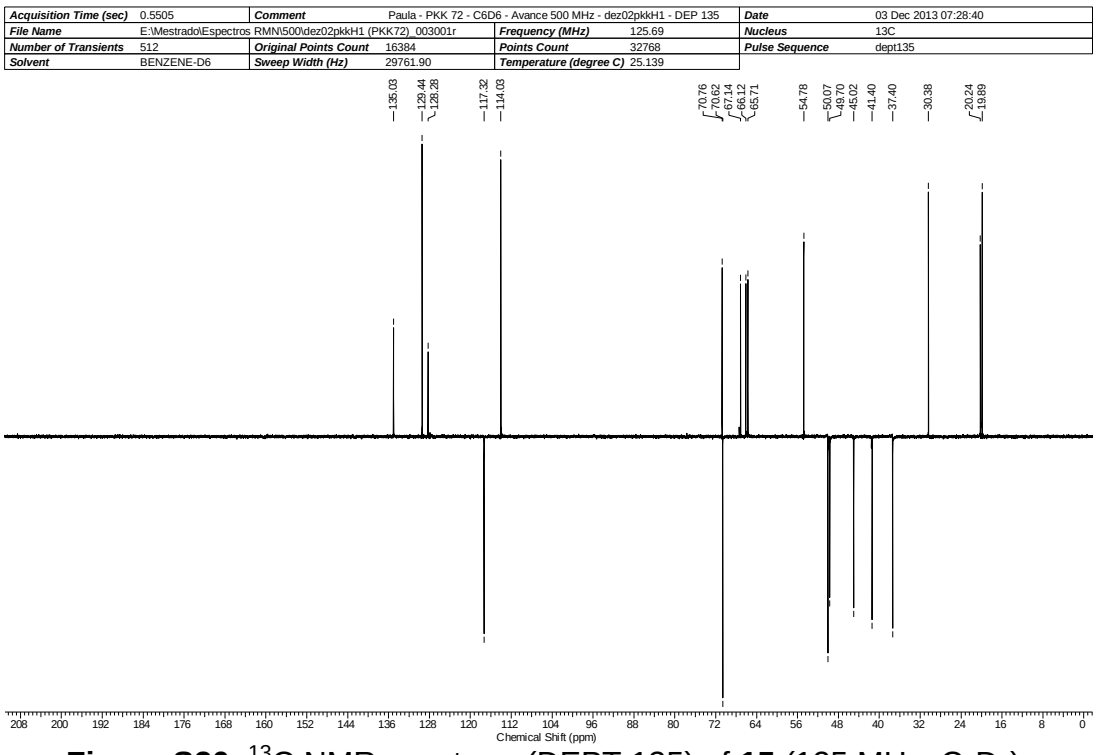
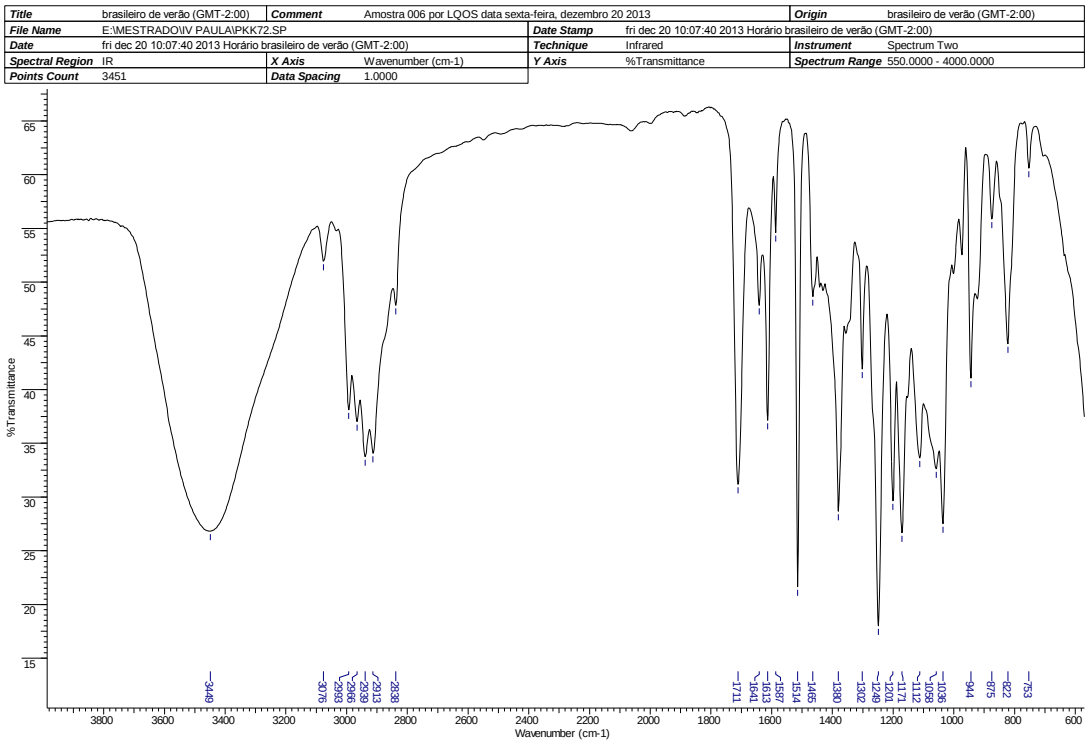


Figure S30. ^{13}C NMR spectrum (DEPT 135) of **15** (125 MHz; C_6D_6).



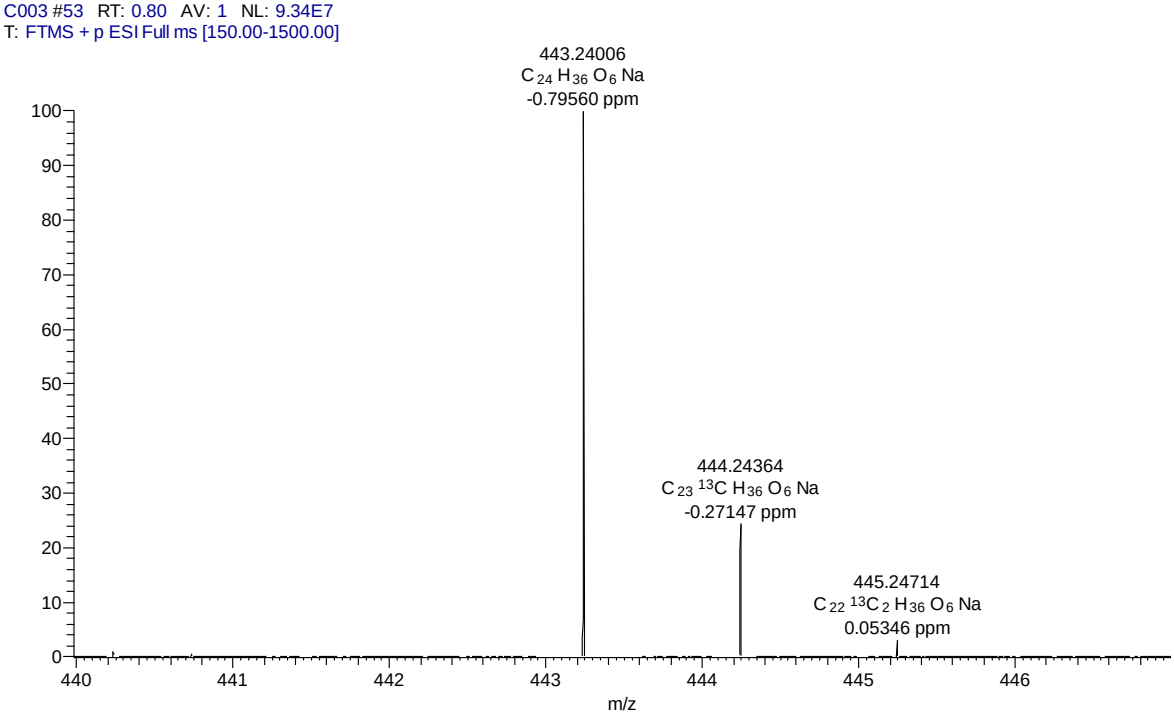


Figure S31. IR and HRMS spectra of **15**.

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Number of Transients	16	***Original Points Count***	16384	***Points Count***	65536	***Pulse Sequence***	zg30
Solvent	CHLOROFORM-D	***Sweep Width (Hz)***	10000.00	***Temperature (degree C)***	25.138		

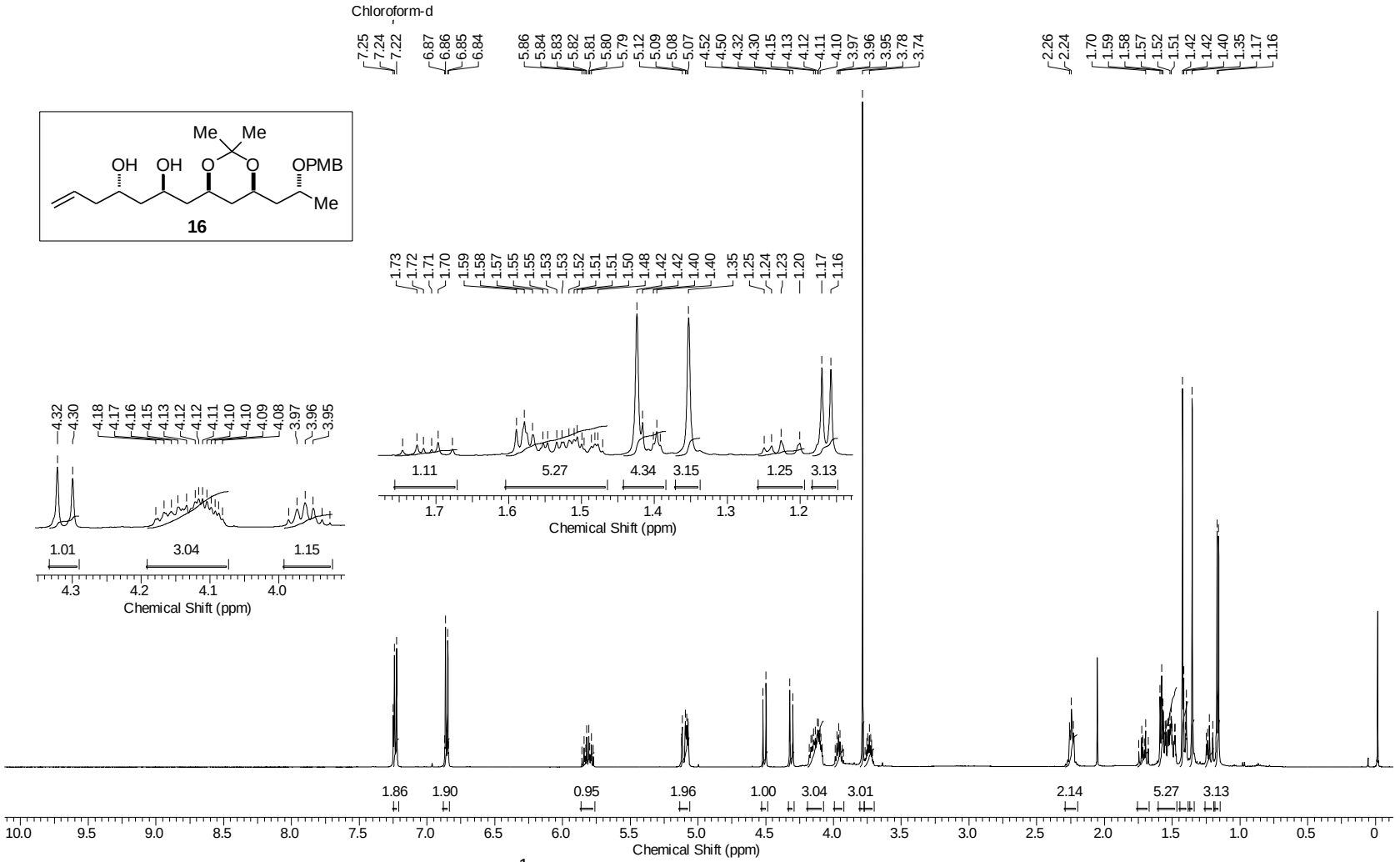


Figure S32. ^{1}H NMR spectrum of **16** (500 MHz; $CDCl_3$).

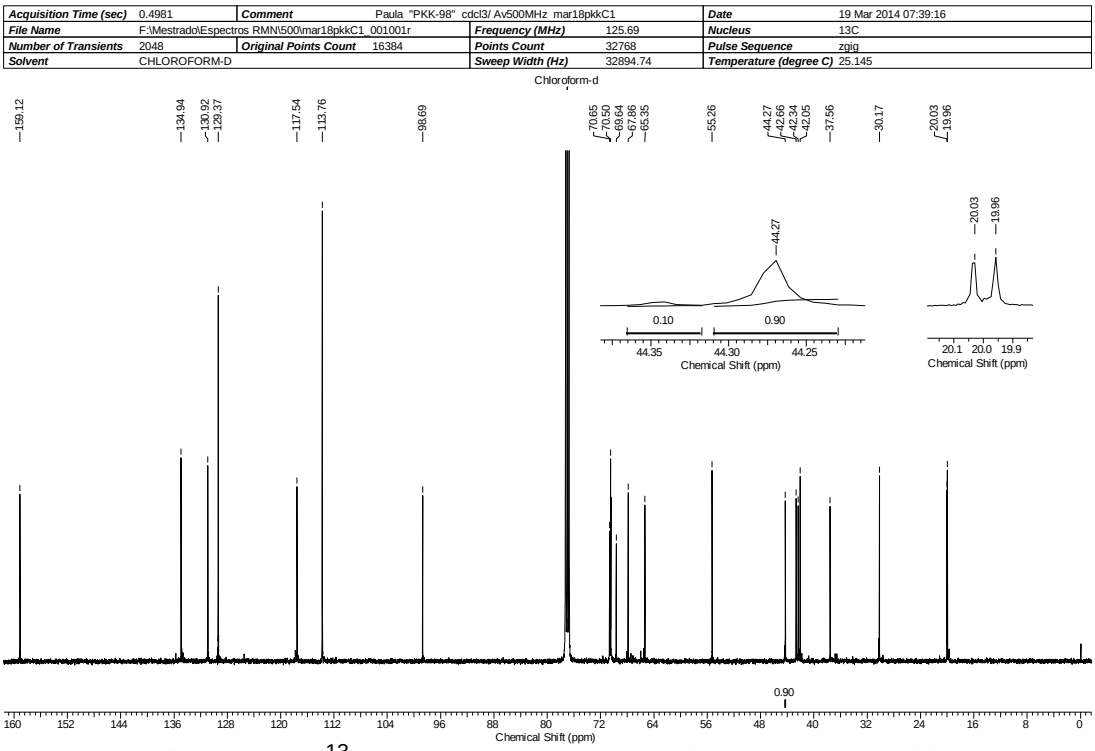


Figure S33. ^{13}C NMR spectrum of **16** (125 MHz; $CDCl_3$).

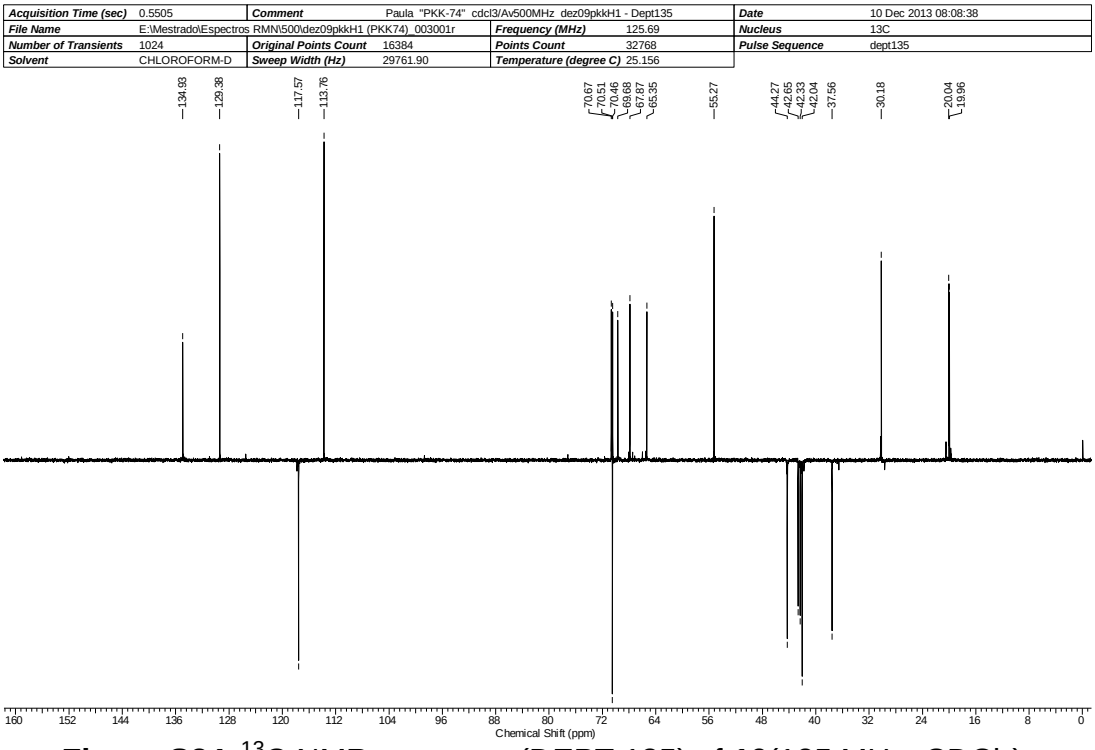
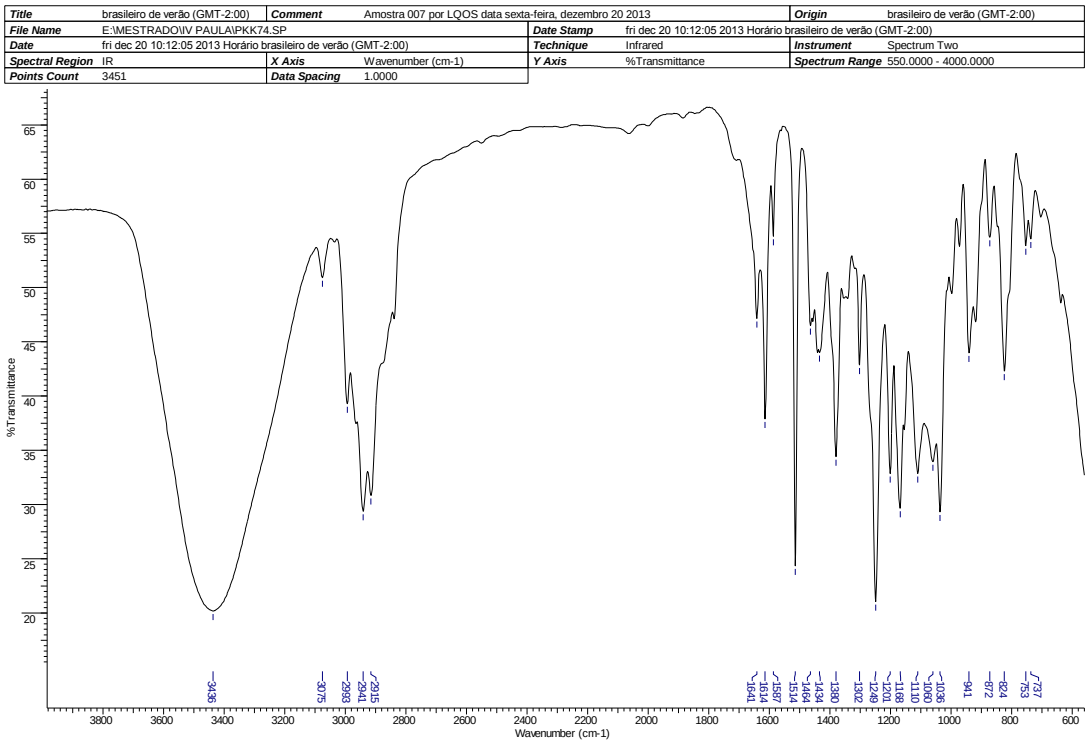


Figure S34. ^{13}C NMR spectrum (DEPT 135) of **16**(125 MHz; $CDCl_3$).



C004 #20 RT: 0.30 AV: 1 NL: 1.04E8
T: FTMS + p ESI Full ms [150.00-1500.00]

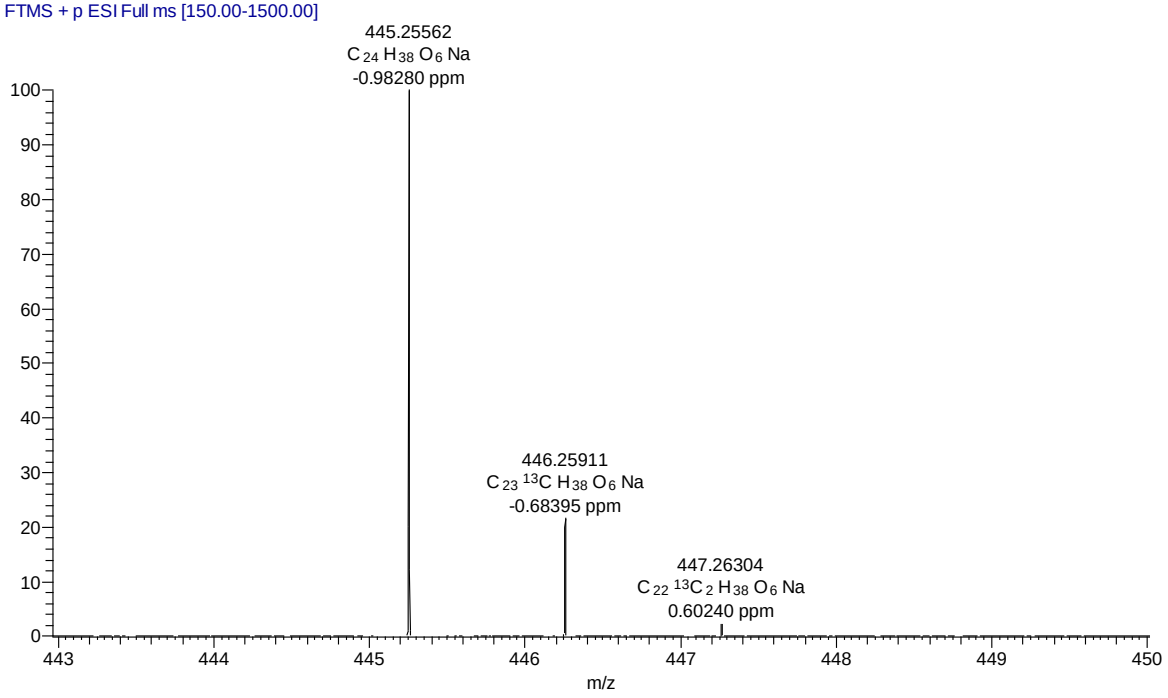


Figure S35. IR and HRMS spectra of **16**.

Acquisition Time (sec)	1.6384	***Comment***	Paula - PKK99 - CDCl3 - Av 500 MHz - mar20pkkH2			***Date***	20 Mar 2014 10:54:36
File Name	F:\Mestrado\Espectros RMN\500\mar20pkkH2 (PKK99)_001001r			***Frequency (MHz)***	499.87	***Nucleus***	1H
Number of Transients	16	***Original Points Count***	16384	***Points Count***	65536	***Pulse Sequence***	zg30
Solvent	CHLOROFORM-D	***Sweep Width (Hz)***	10000.00	***Temperature (degree C)***	25.151		

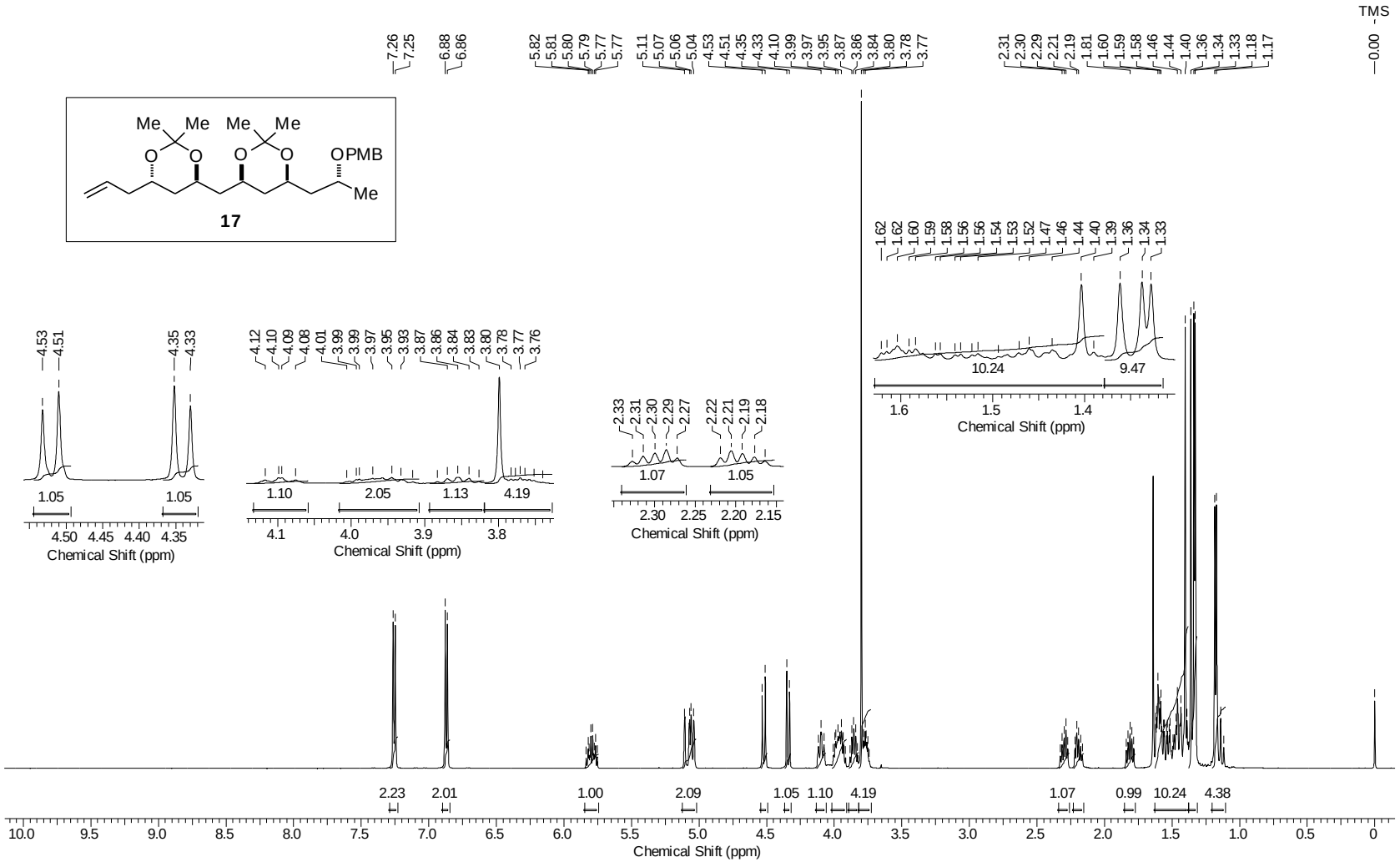


Figure S36. ^{1}H NMR spectrum of **17** (500 MHz; $CDCl_3$).

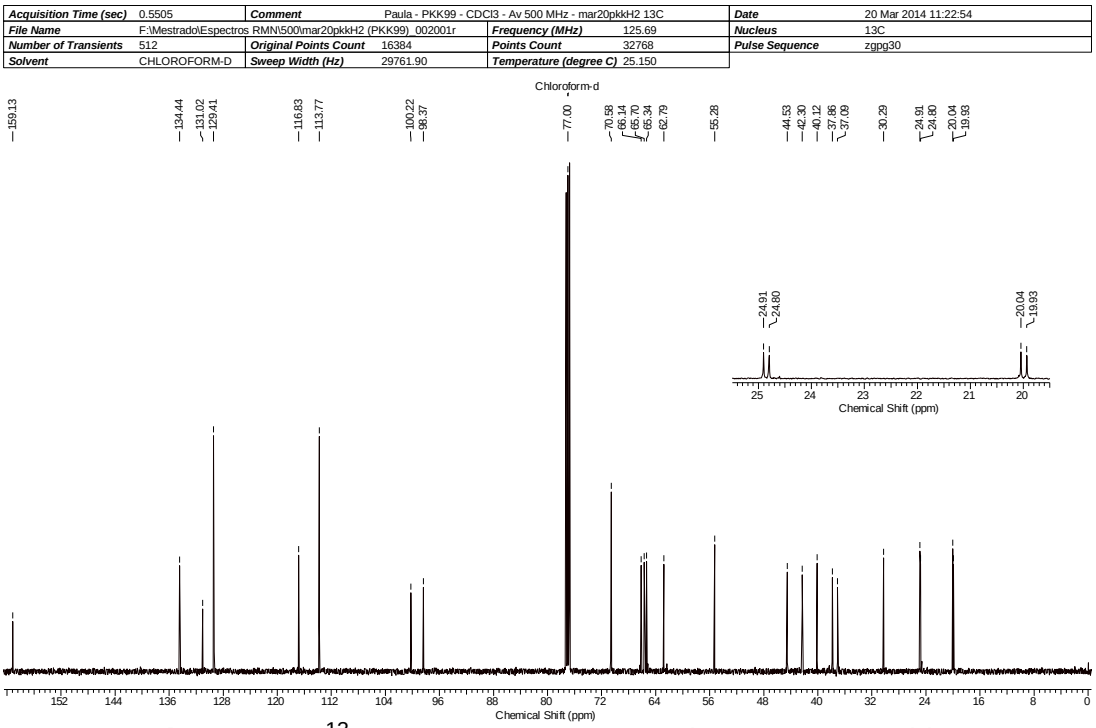


Figure S37. ^{13}C NMR spectrum of **17** (125 MHz; $CDCl_3$).

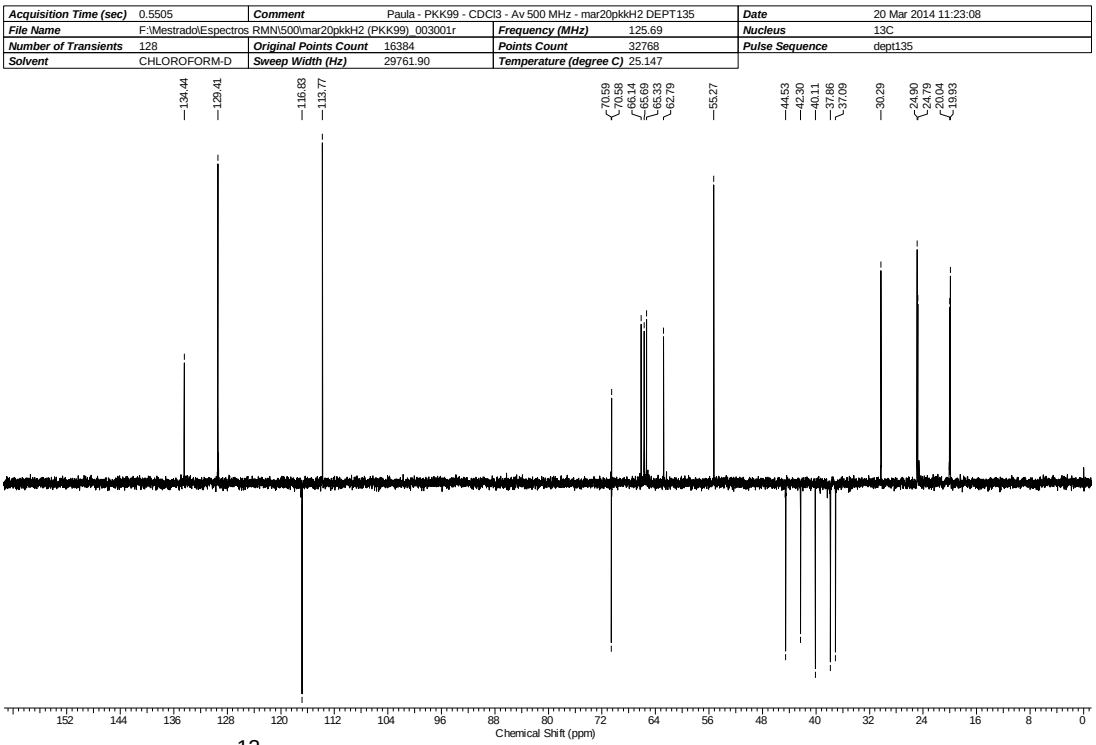
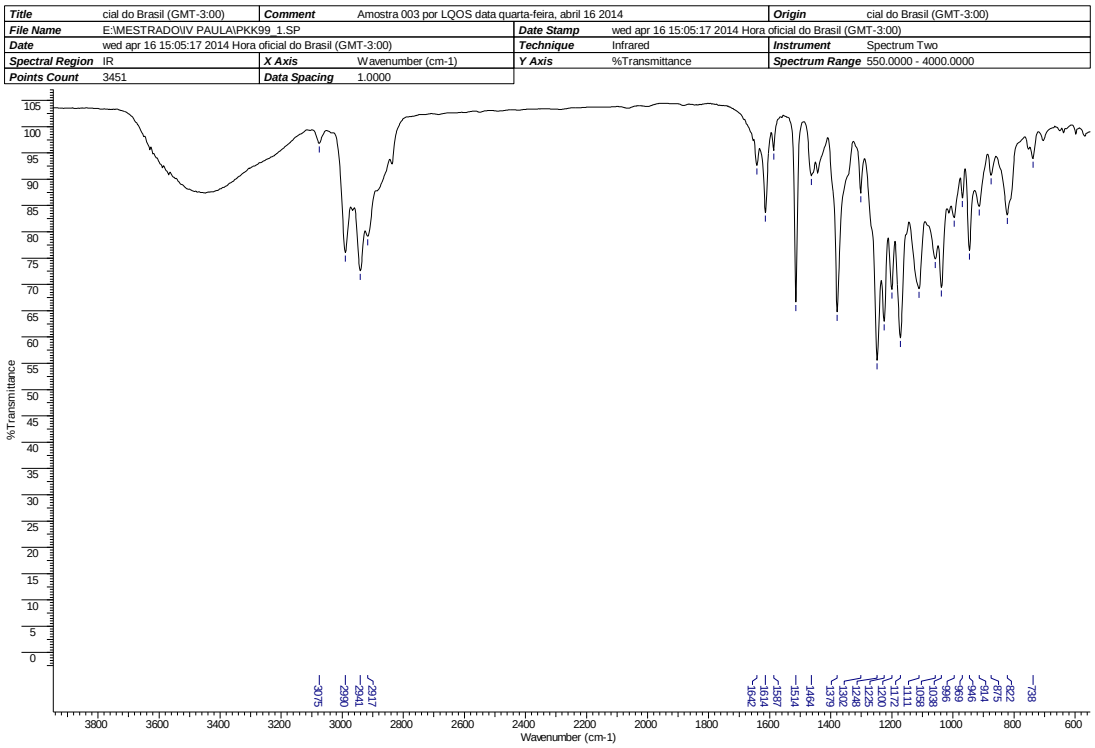


Figure S38. ^{13}C NMR spectrum (DEPT 135) of **17** (125 MHz; $CDCl_3$).



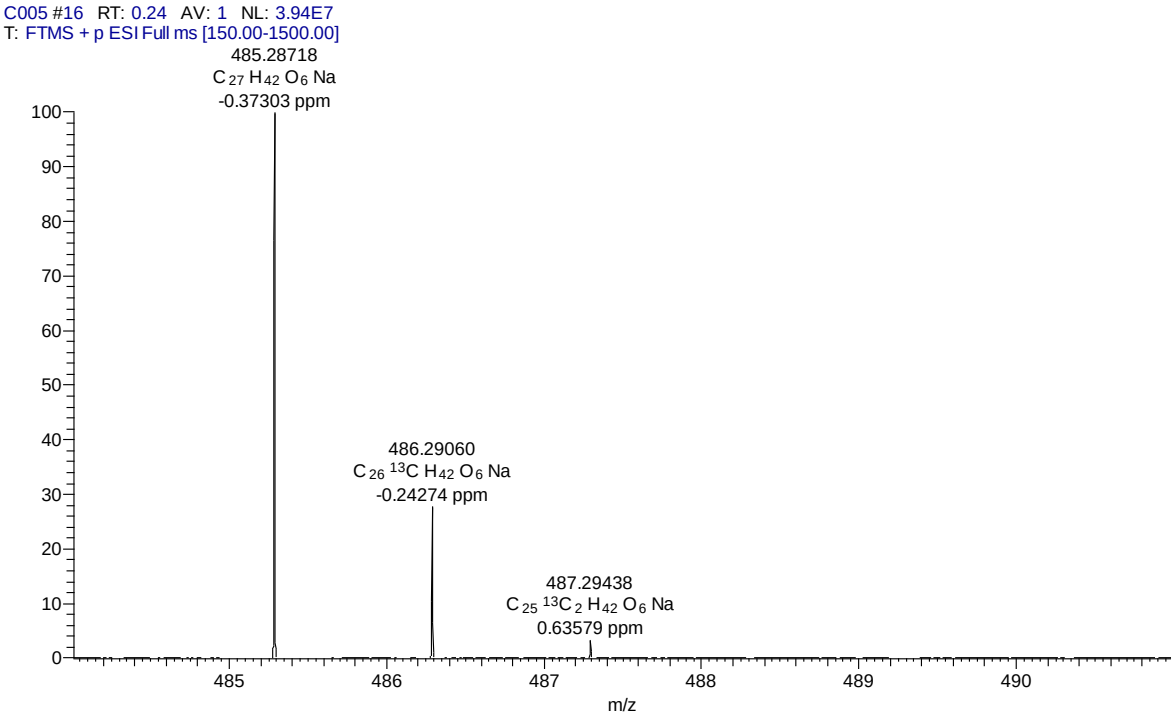


Figure S39. IR and HRMS spectra of **17**.

Acquisition Time (sec)	1.6384	***Comment***	Paula "PKK-102" cd3od/Av500MHz mar25pkkH2			***Date***	26 Mar 2014 07:34:36
File Name	\\nmrsparc.iqm.unicamp.br\espectros\avance500\2014\mar14\Luiz Carlos\mar25pkkH2_001001r					***Frequency (MHz)***	499.87
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	16384	***Points Count***	65536
Pulse Sequence	zg30	***Solvent***	MeOD	***Sweep Width (Hz)***	10000.00	***Temperature (degree C)***	25.147

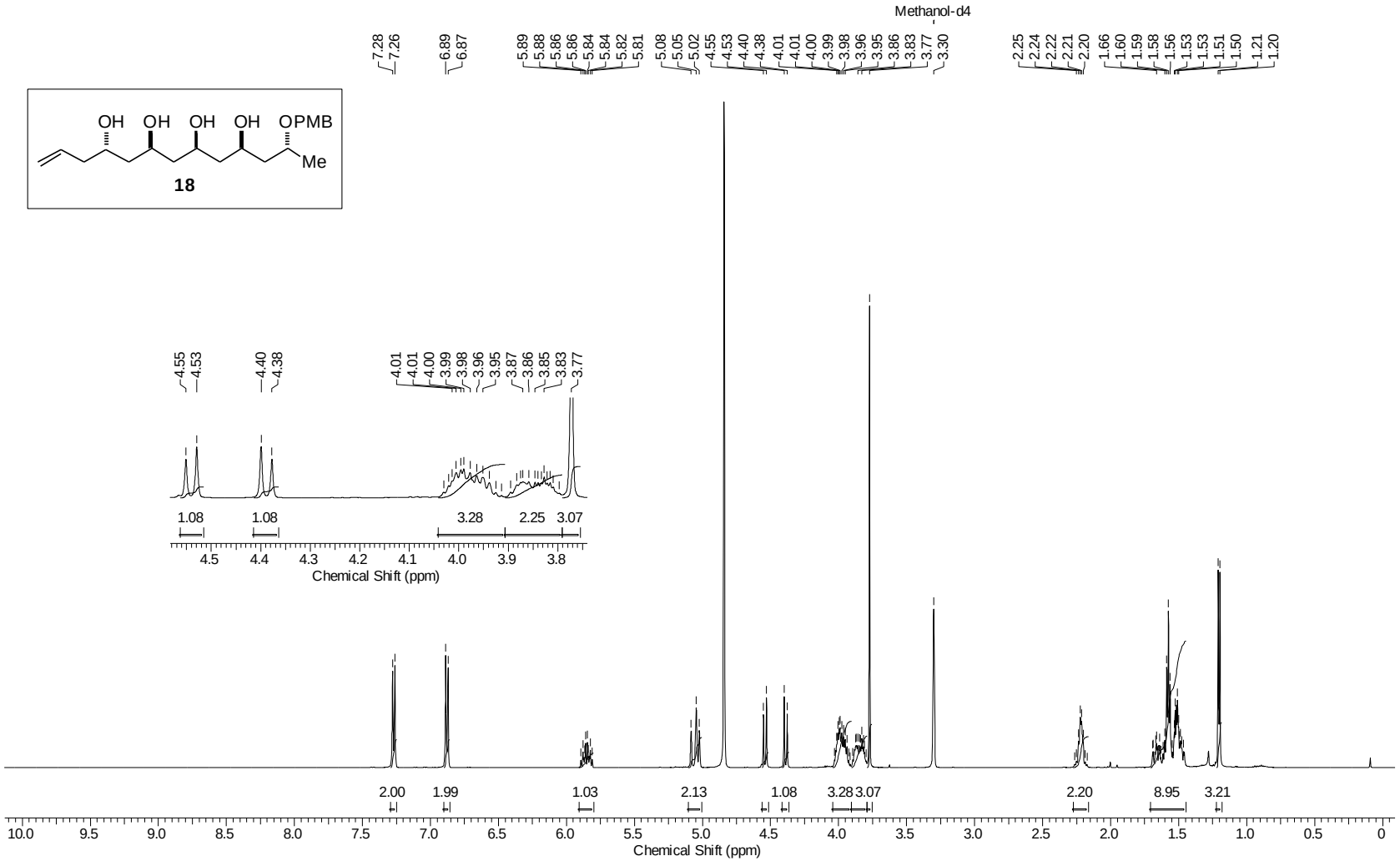


Figure S40. ^{1}H NMR spectrum of **18** (500 MHz; MeOD).

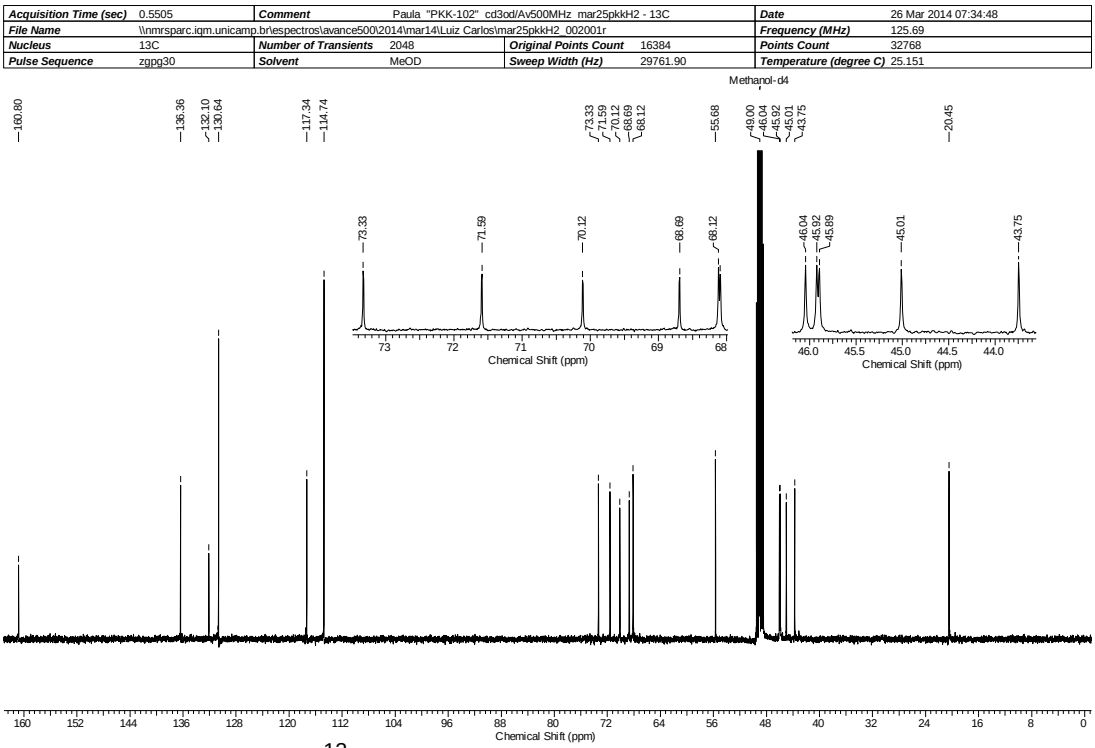


Figure S41. ^{13}C NMR spectrum of **18** (125 MHz; MeOD).

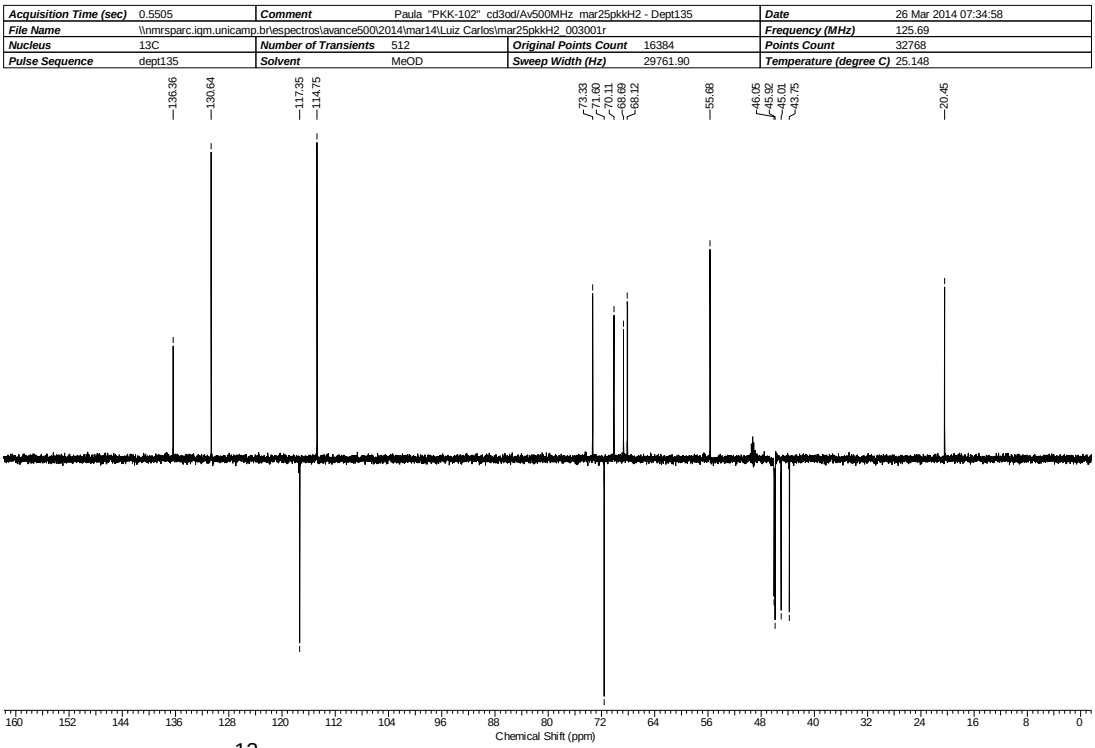


Figure S42. ^{13}C NMR spectrum (DEPT 135) of **18** (125 MHz; MeOD).

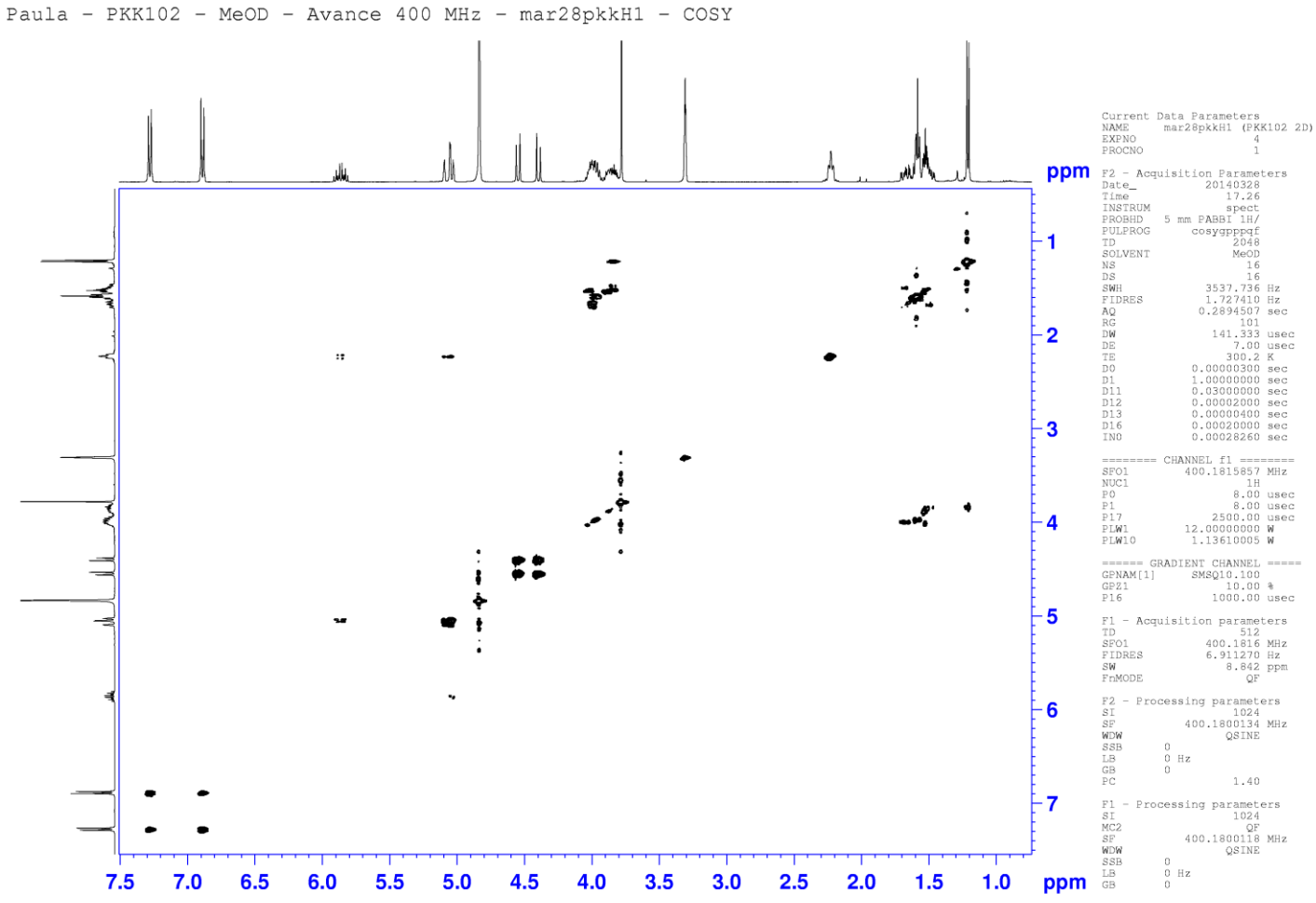


Figure S43. COSY contour map for **18**.

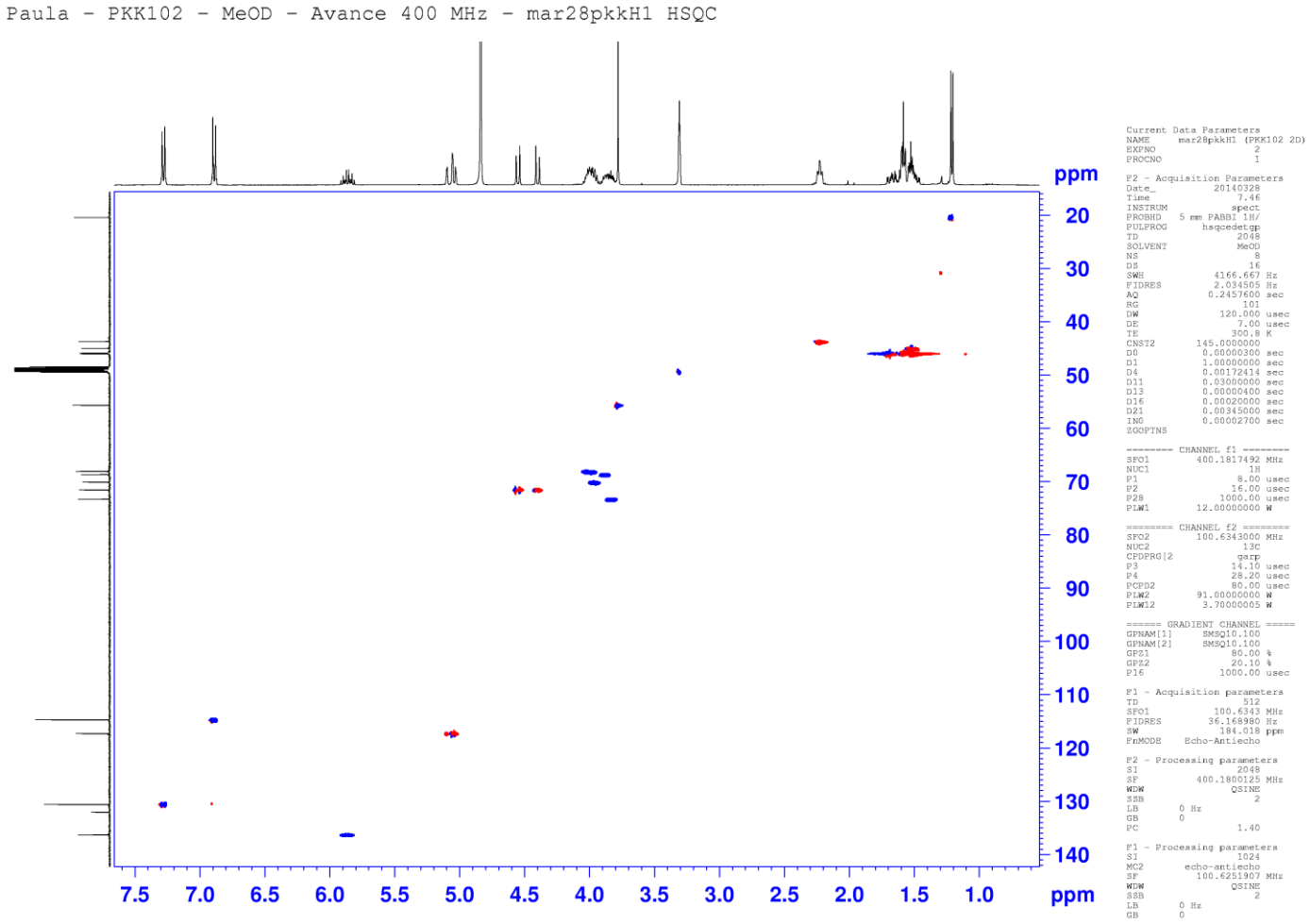


Figure S44. HSQC contour map for **18**.

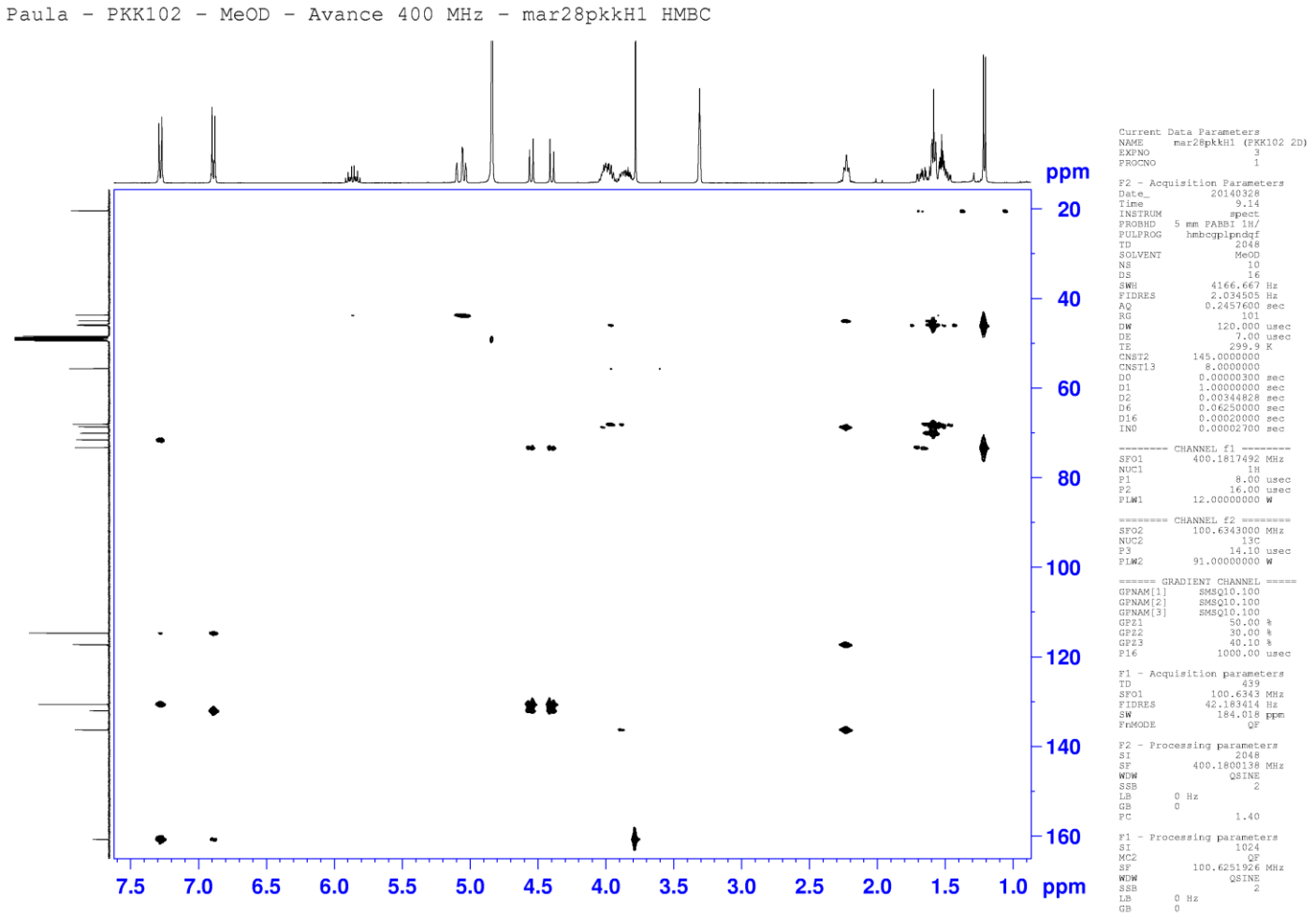
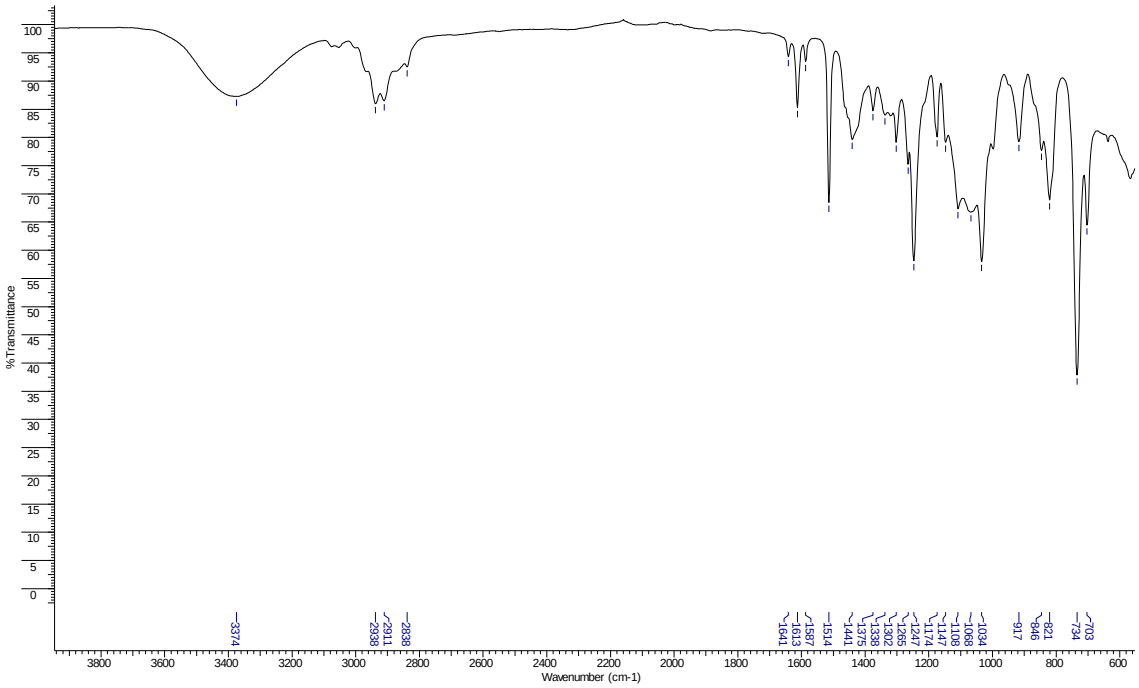


Figure S45. HMBC contour map for **18**.

Title	cial do Brasil (GMT-3:00)	**Comment**	Amostra 001 por LQOS data sexta-feira, outubro 17 2014			**Origin**	cial do Brasil (GMT-3:00)
File Name	E:\MESTRADO\IV PAULA\PKK102.SP			**Date Stamp**	fri oct 17 17:06:12 2014 Hora oficial do Brasil (GMT-3:00)		
Date	fri oct 17 17:06:12 2014 Hora oficial do Brasil (GMT-3:00)			**Technique**	Infrared	**Instrument**	Spectrum Two
Spectral Region	IR	**X Axis**	Wavenumber (cm-1)	**Y Axis**	%Transmittance	**Spectrum Range**	550.0000 - 4000.0000
Points Count	3451	**Data Spacing**	1.0000				



C008 #33 RT: 0.50 AV: 1 NL: 1.50E8
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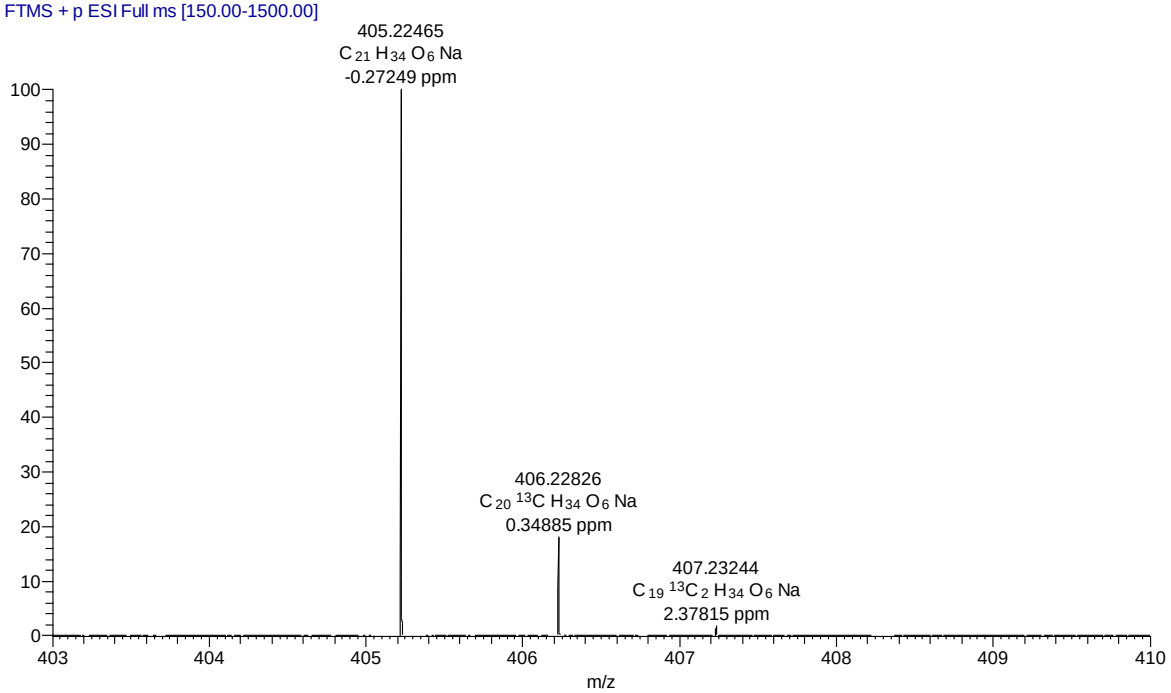


Figure S46. IR and HRMS spectra of **18**.

Acquisition Time (sec)	1.6384	***Comment***	Paula "PKK-100" cdcl3/Av500MHz mar25pkkH1			***Date***	26 Mar 2014 07:34:24
File Name	\\nmrsparc.iqm.unicamp.br\espectros\avance500\2014\mar14\Luiz Carlos\mar25pkkH1_001001r					***Frequency (MHz)***	499.87
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	16384	***Points Count***	65536
Pulse Sequence	zg30	***Solvent***	CHLOROFORM-D	***Sweep Width (Hz)***	10000.00	***Temperature (degree C)***	25.150

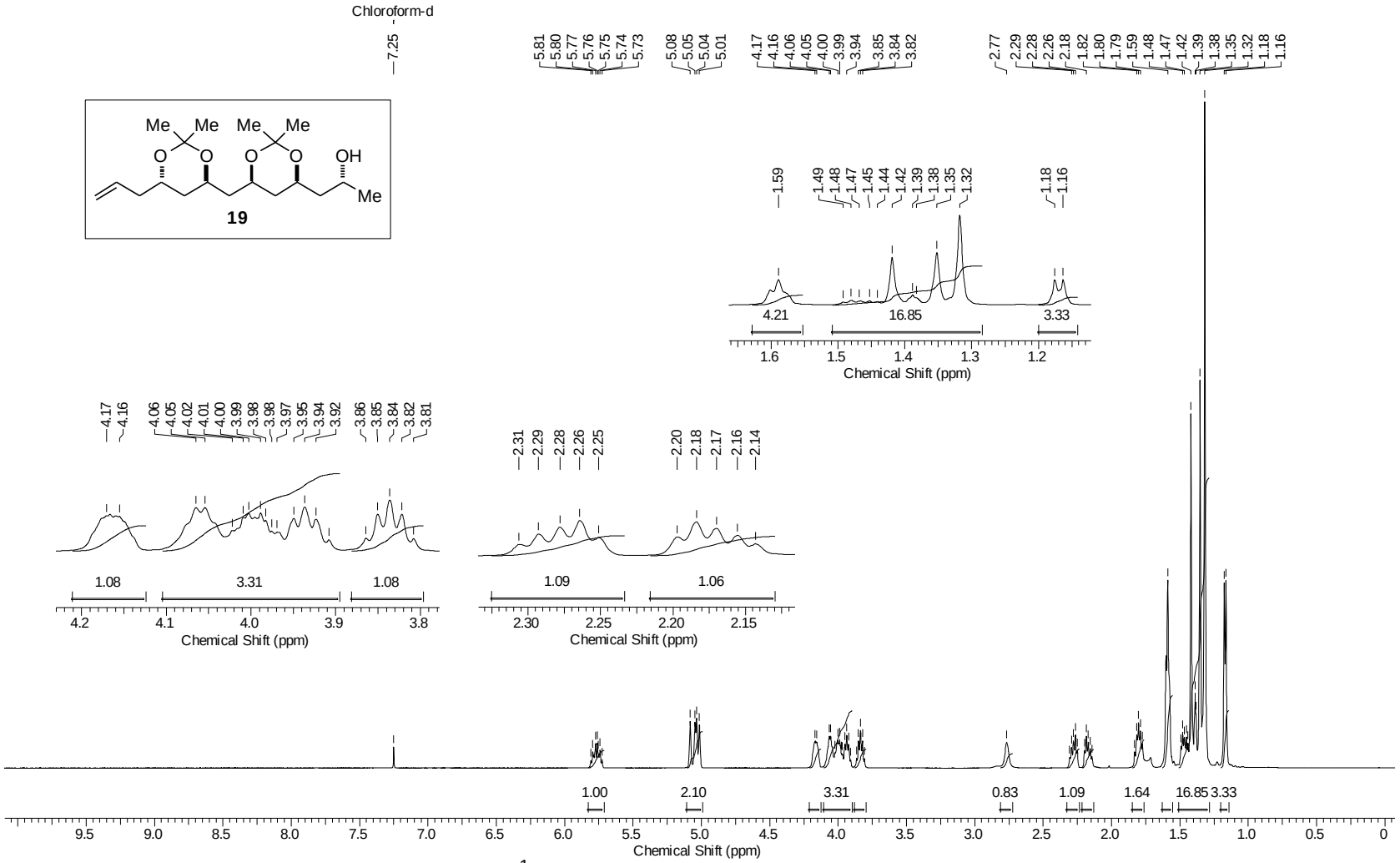


Figure S47. ^{1}H NMR spectrum of **19** (500 MHz; $CDCl_3$).

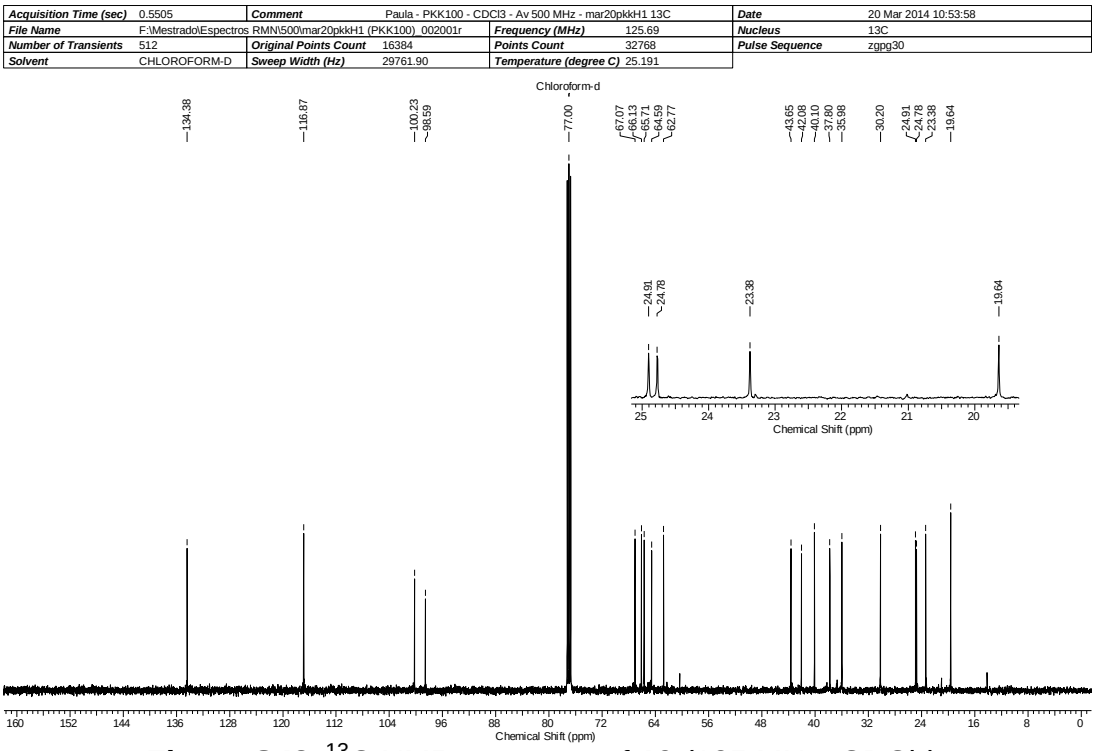


Figure S48. ^{13}C NMR spectrum of **19** (125 MHz; $CDCl_3$).

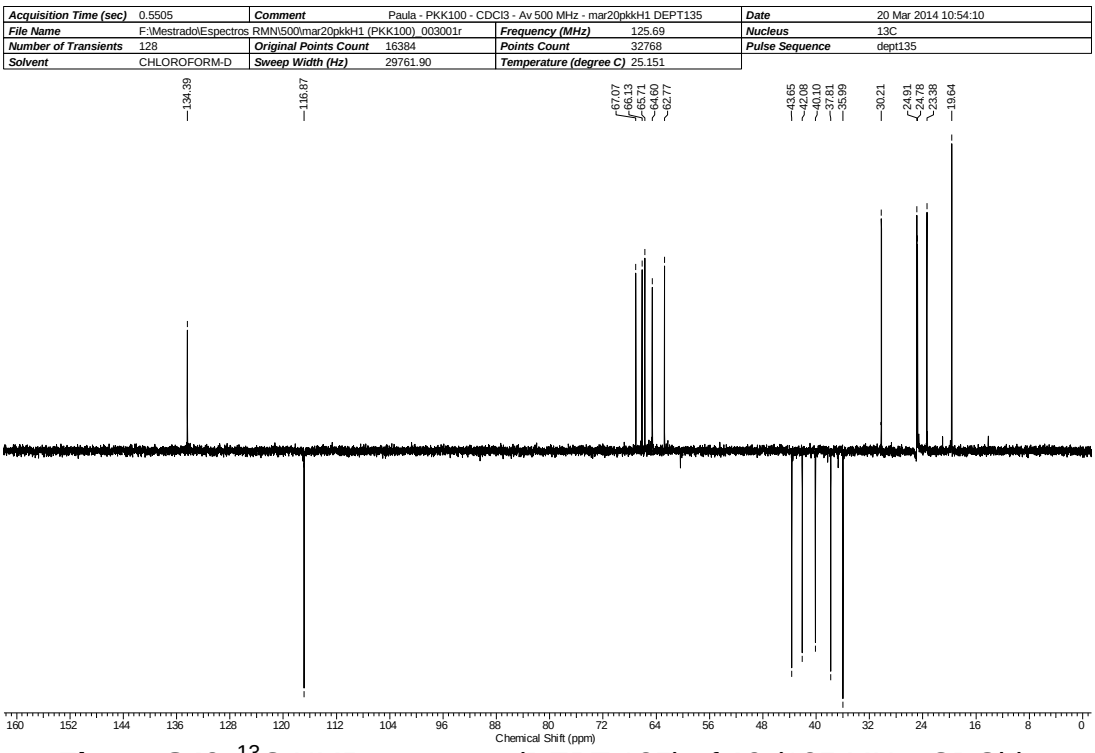
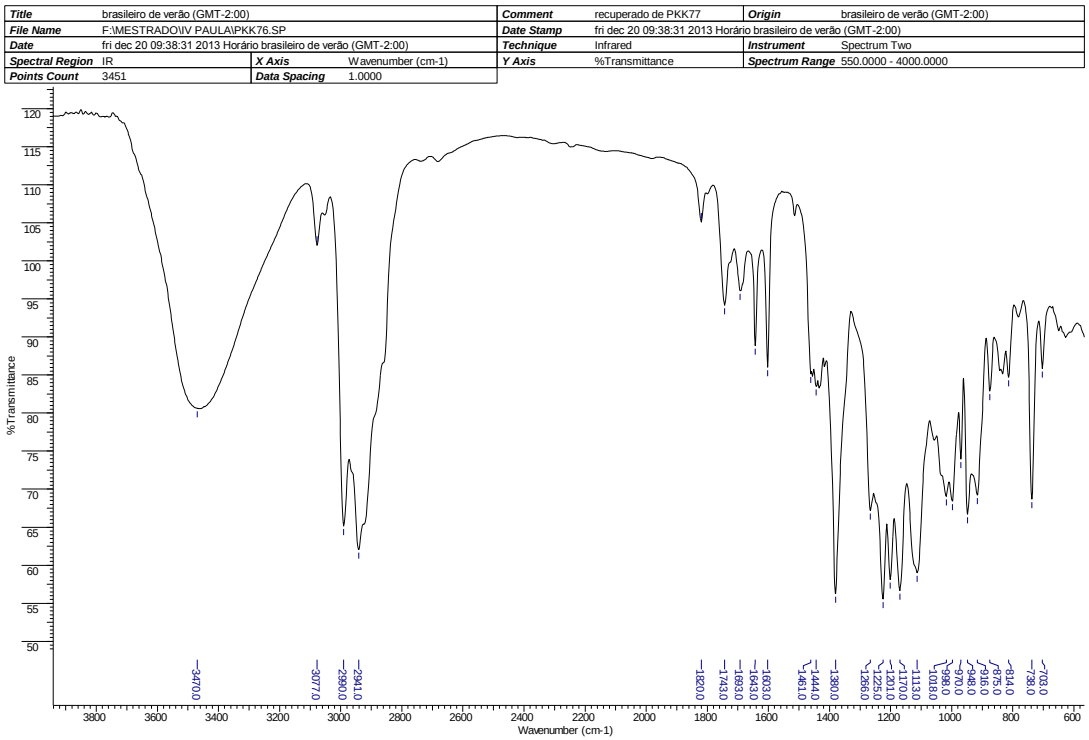


Figure S49. ^{13}C NMR spectrum (DEPT 135) of **19** (125 MHz; $CDCl_3$).



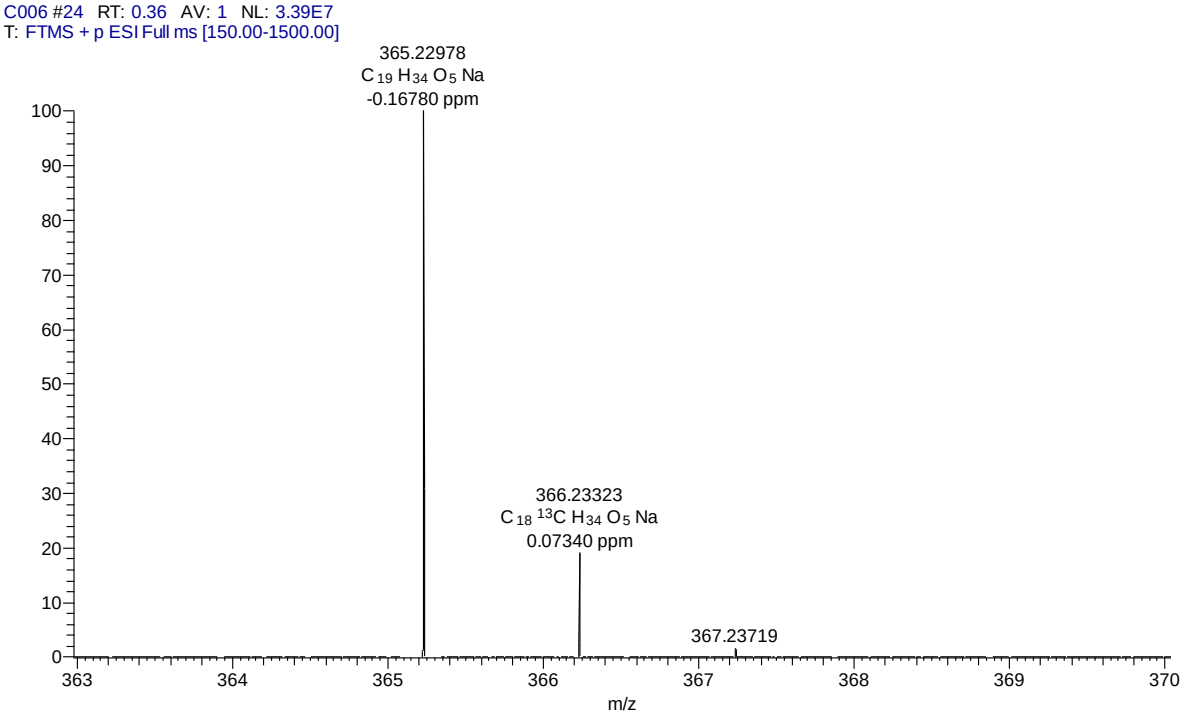


Figure S50. IR and HRMS spectra of **19**.

Acquisition Time (sec)	2.6564	***Date***	07 Jan 2014 14:25:18				
File Name	\\nmrsparc.iqm.unicamp.br\espectros\avance600\2014\jan14\Luiz Carlos\jan07pkkH1_001001r					***Frequency (MHz)***	600.17
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	32768	***Points Count***	65536
Pulse Sequence	zg30	***Solvent***	CHLOROFORM-D			***Sweep Width (Hz)***	12335.53
Temperature (degree C)	25.150						

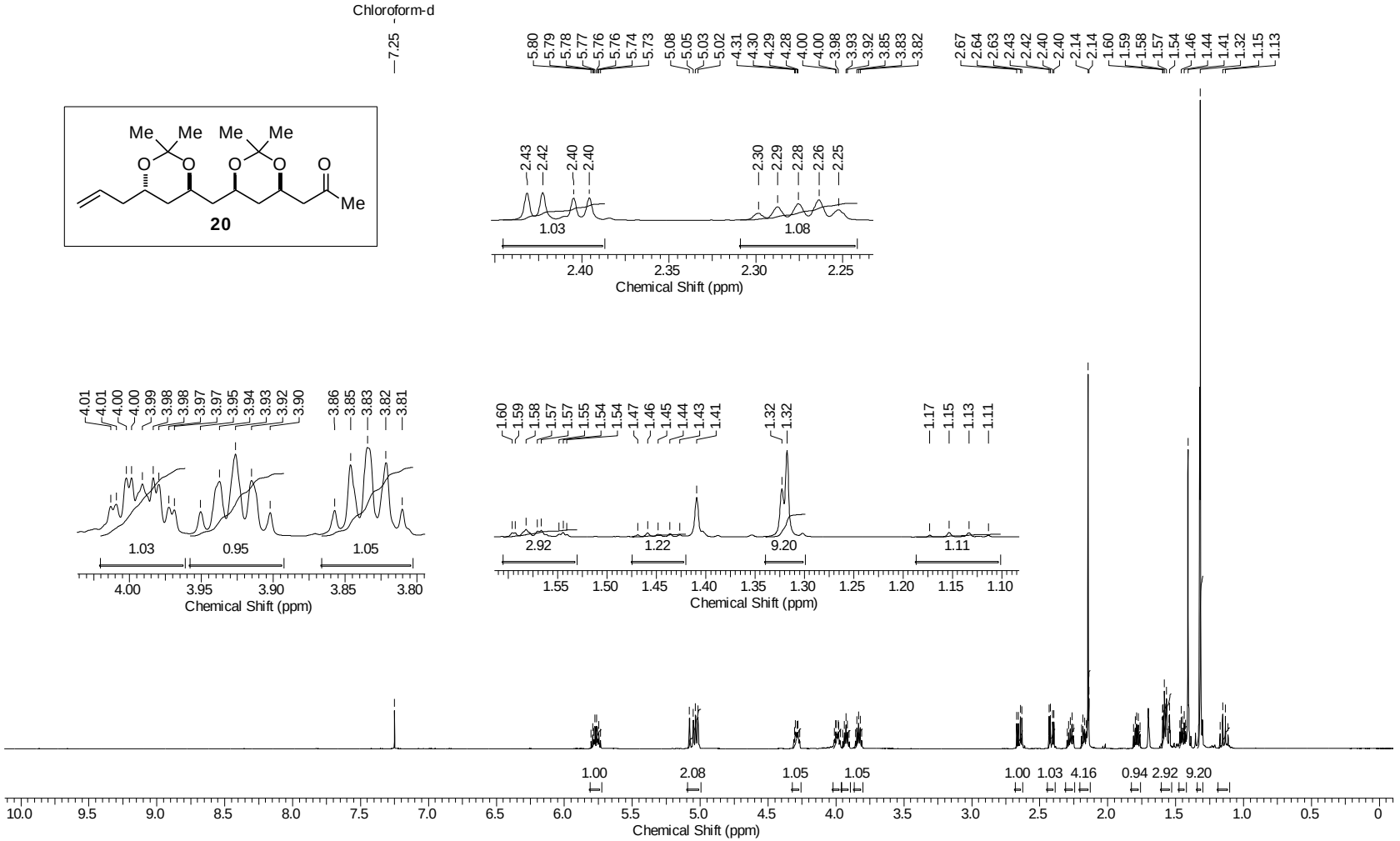


Figure S51. ^{1}H NMR spectrum of **20** (600 MHz; $CDCl_3$).

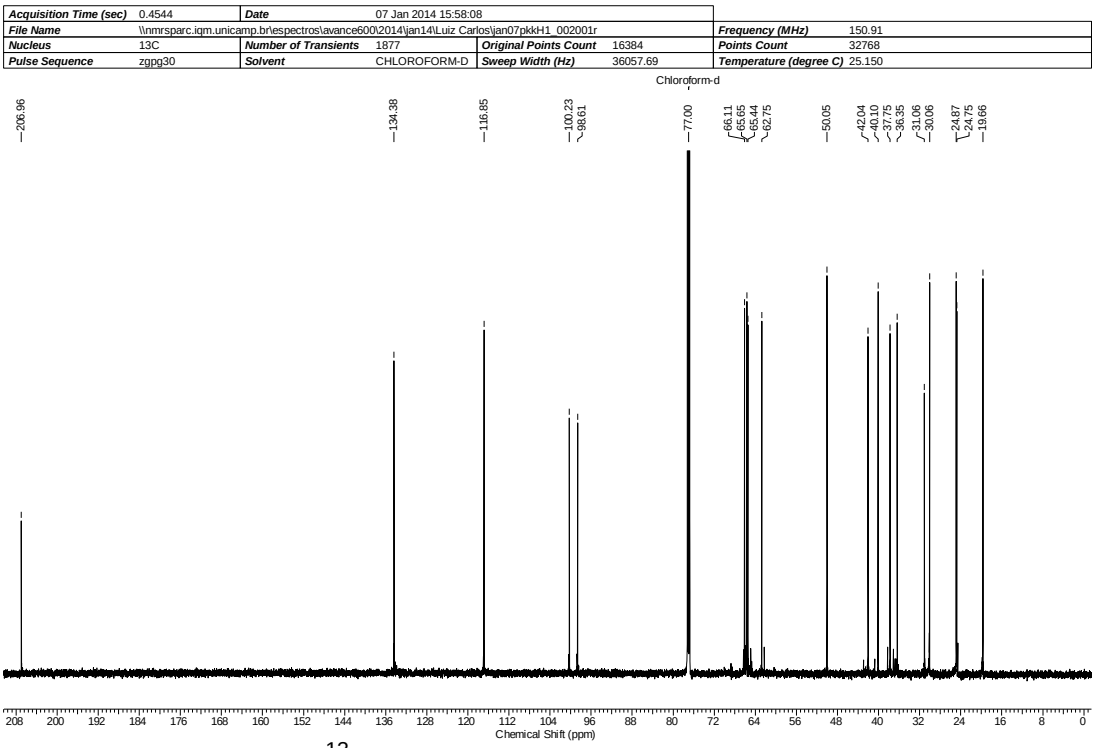


Figure S52. ^{13}C NMR spectrum of **20** (150 MHz; $CDCl_3$).

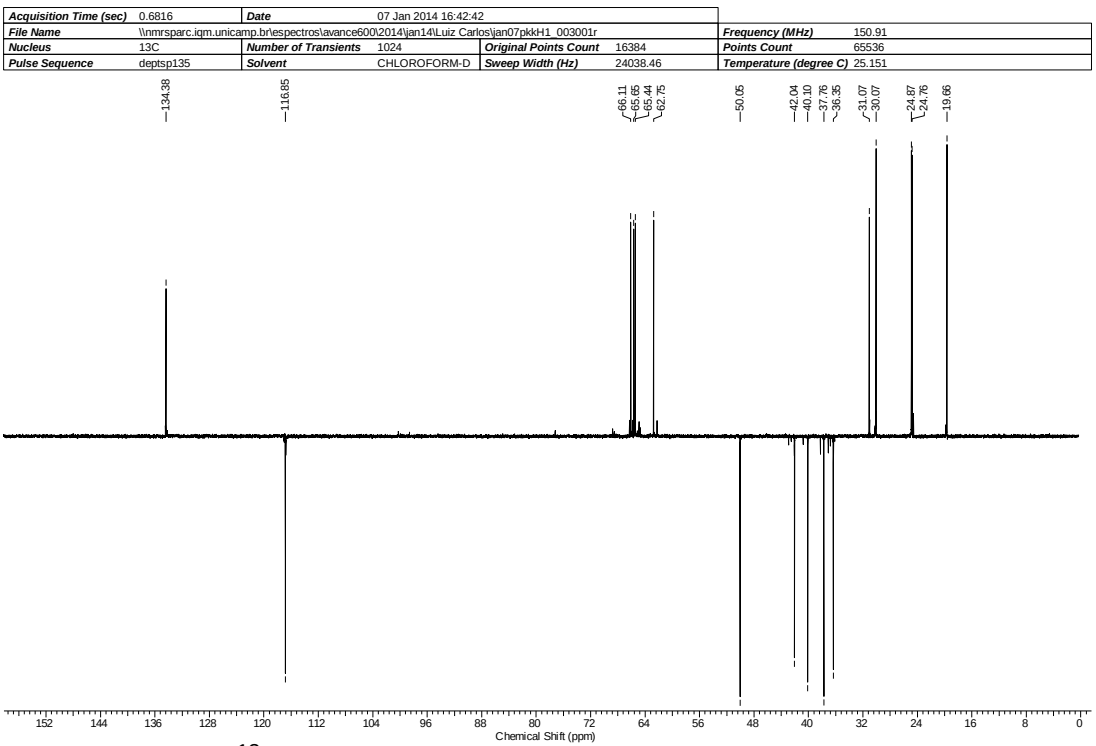
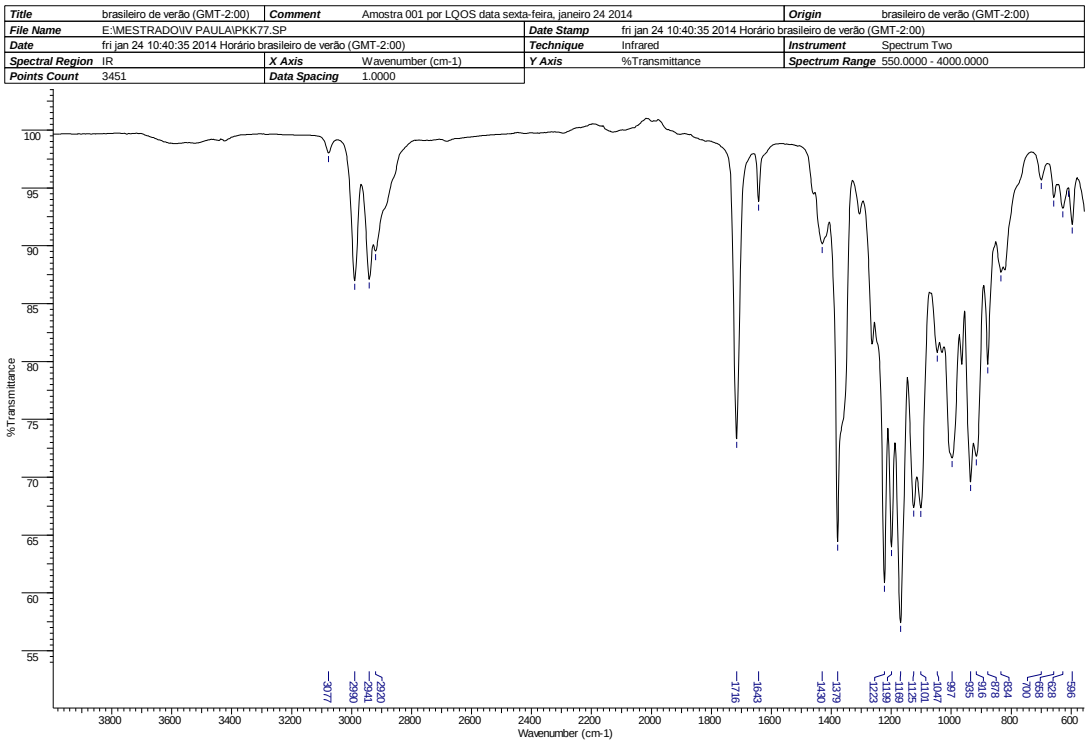


Figure S53. ^{13}C NMR spectrum (DEPT 135) of **20** (150 MHz; $CDCl_3$).



C007 #8 RT: 0.12 AV: 1 NL: 5.81E7
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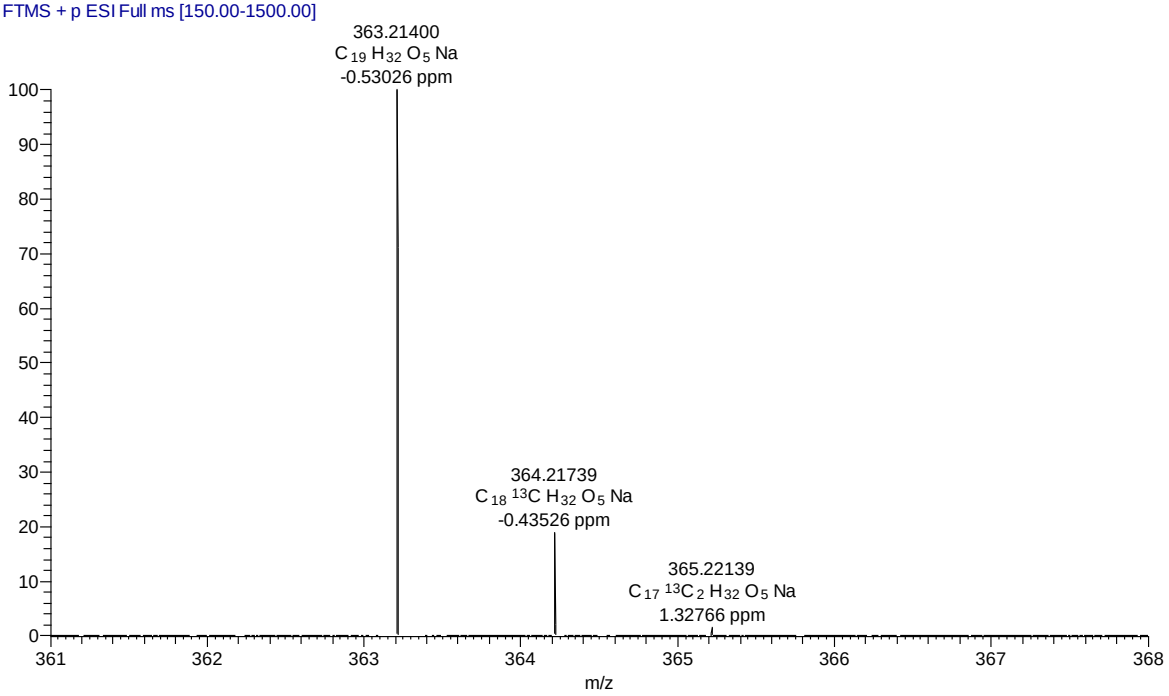


Figure S54. IR and HRMS spectra of **20**.

Acquisition Time (sec)	3.1654	***Comment***	PKK82 CDCl3 250MHz jan16pkkH1			***Date***	16 Jan 2014 20:02:30
File Name	F:\Mestrado\Espectros RMN\250\jan16pkkH1 (PKK82)_001001r			***Frequency (MHz)***	250.13	***Nucleus***	1H
Number of Transients	16	***Original Points Count***	16384	***Points Count***	32768	***Pulse Sequence***	zg30
Solvent	CHLOROFORM-D			***Sweep Width (Hz)***	5175.98	***Temperature (degree C)***	24.060

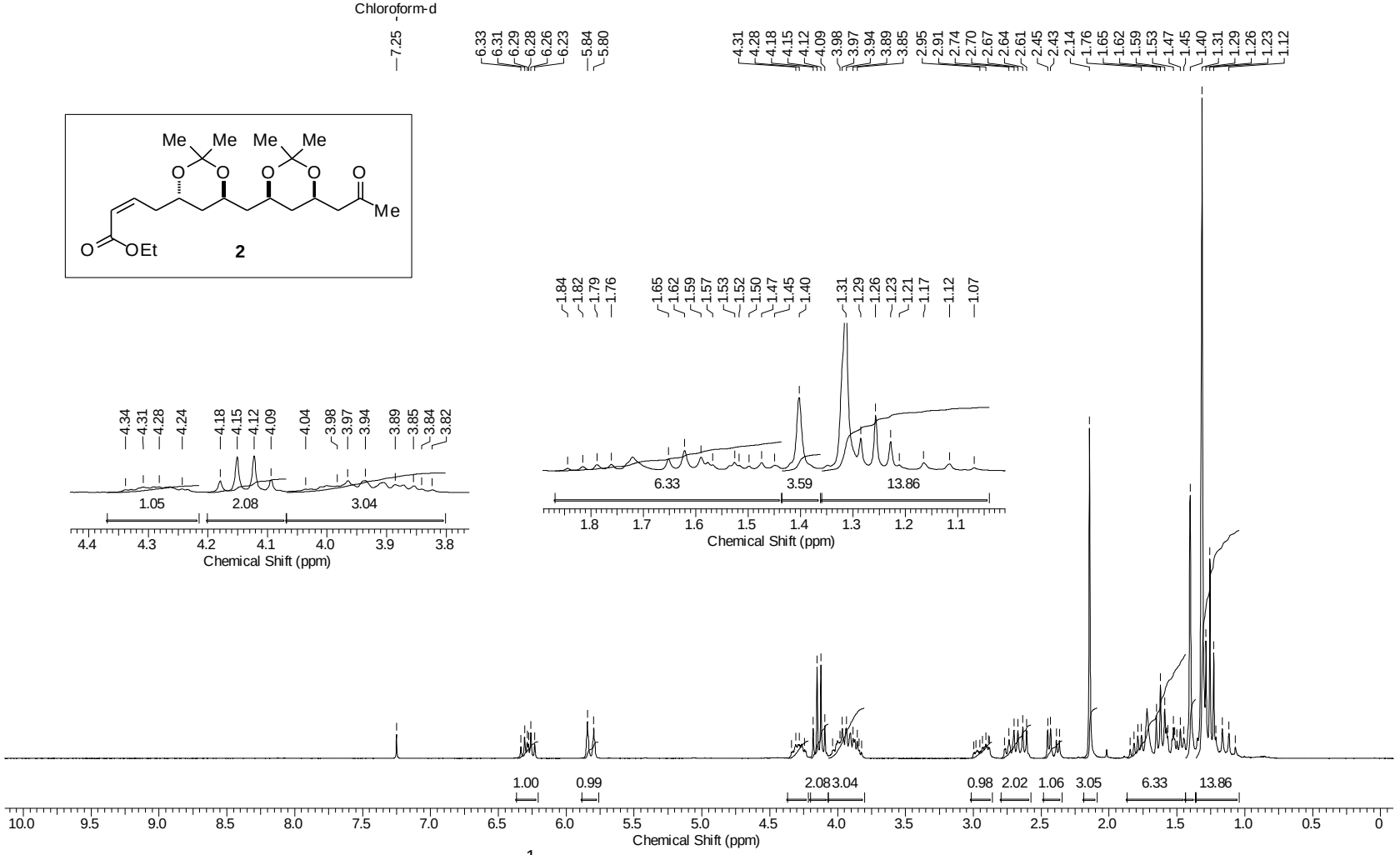


Figure S55. ^{1}H NMR spectrum of **2** (250 MHz; $CDCl_3$).

Acquisition Time (sec)	0.5439	***Comment***	PKK82 CDCl3 250MHz jan16pkkC1	***Date***	24 Jan 2014 11:16:36
File Name	F:\Mestrado\Espectros RMN\250\jan16pkkC1 (PKK82)correto_002001r			***Frequency (MHz)***	62.90
Nucleus	13C	***Number of Transients***	18863	***Original Points Count*** 8192	***Points Count*** 32768
Pulse Sequence	zgpg30	***Solvent***	CHLOROFORM-D		***Sweep Width (Hz)*** 15060.24
Temperature (degree C)	25.060				

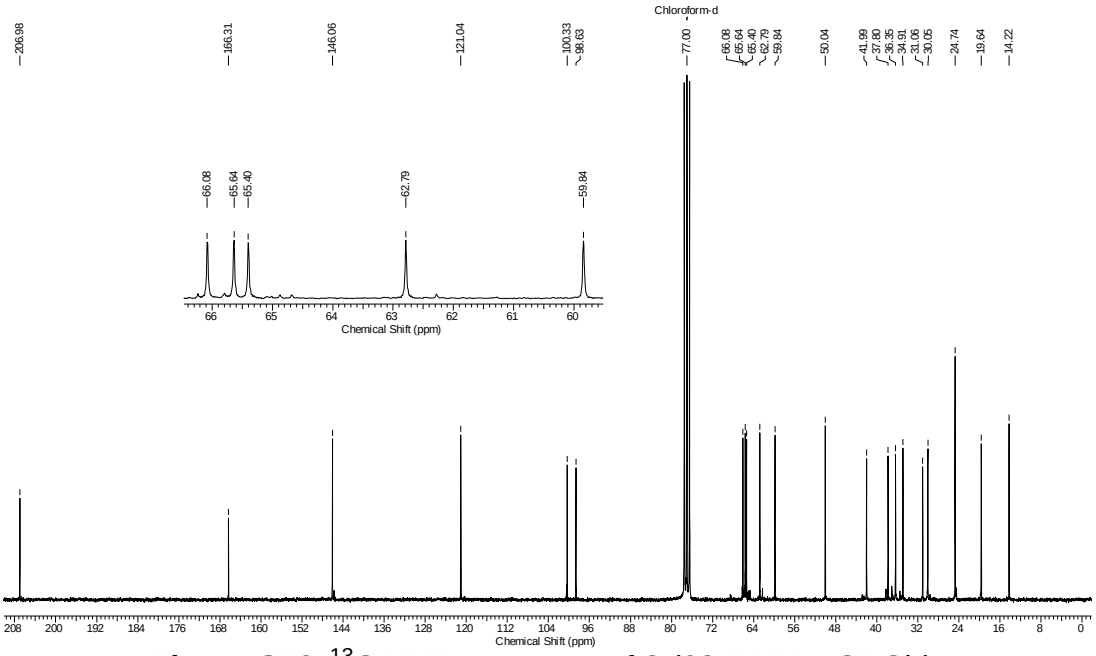


Figure S56. ^{13}C NMR spectrum of **2** (62.5 MHz; $CDCl_3$).

Acquisition Time (sec)	0.5439	***Comment***	PKK82 CDCl3 250MHz jan16pkkC1 dept135	***Date***	24 Jan 2014 11:16:18
File Name	F:\Mestrado\Espectros RMN\250\jan16pkkC1 (PKK82)correto_001001r			***Frequency (MHz)***	62.90
Nucleus	13C	***Number of Transients***	1024	***Original Points Count*** 8192	***Points Count*** 32768
Pulse Sequence	dept135	***Solvent***	CHLOROFORM-D	***Sweep Width (Hz)*** 15060.24	***Temperature (degree C)*** 24.160

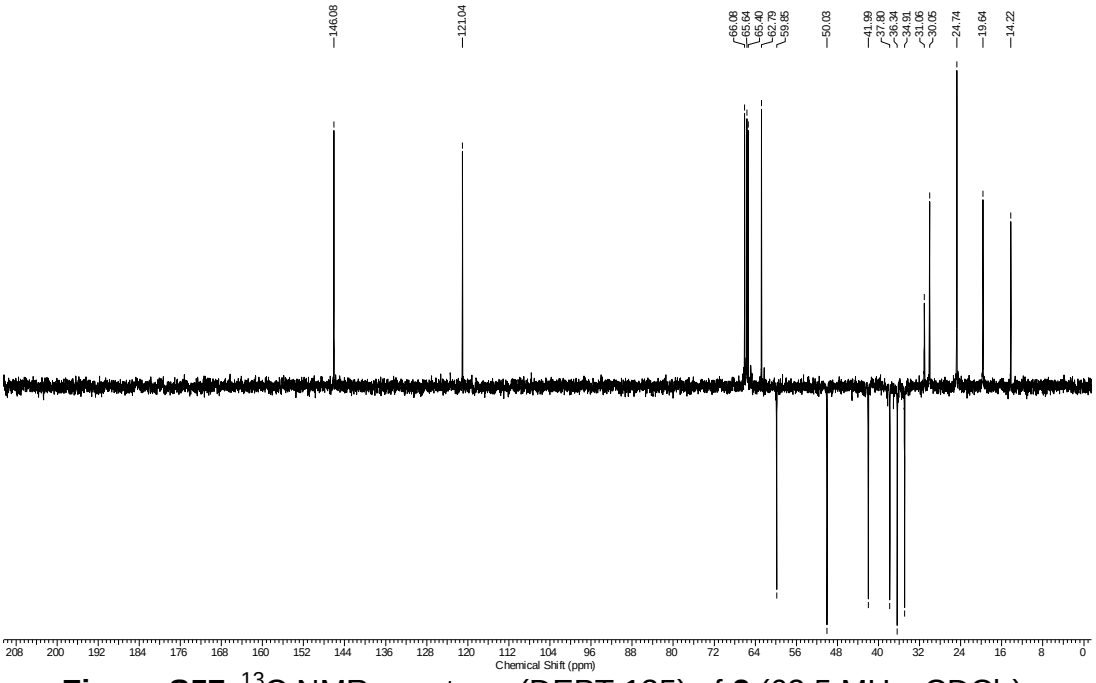
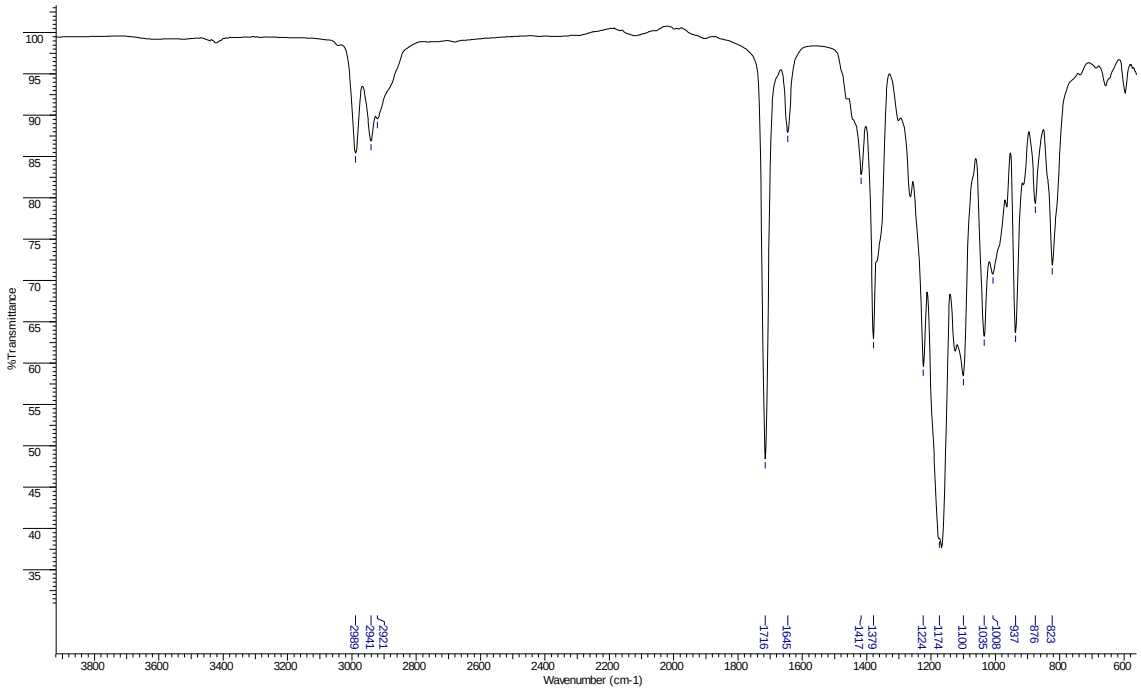


Figure S57. ^{13}C NMR spectrum (DEPT 135) of **2** (62.5 MHz; $CDCl_3$).

Title	cial do Brasil (GMT-3:00)	***Comment***	Amostra 002 por LQOS data sexta-feira, outubro 17 2014			***Origin***	cial do Brasil (GMT-3:00)
File Name	E:\MESTRADO\IV PAULA\PKK112.SP			***Date Stamp***	fri oct 17 17:12:21 2014 Hora oficial do Brasil (GMT-3:00)		
Date	fri oct 17 17:12:21 2014 Hora oficial do Brasil (GMT-3:00)			***Technique***	Infrared	***Instrument***	Spectrum Two
Spectral Region	IR	***X Axis***	Wavenumber (cm-1)	***Y Axis***	%Transmittance	***Spectrum Range***	550.0000 - 4000.0000
Points Count	3451	***Data Spacing***	1.0000				



C009 #7 RT: 0.10 AV: 1 NL: 2.37E6
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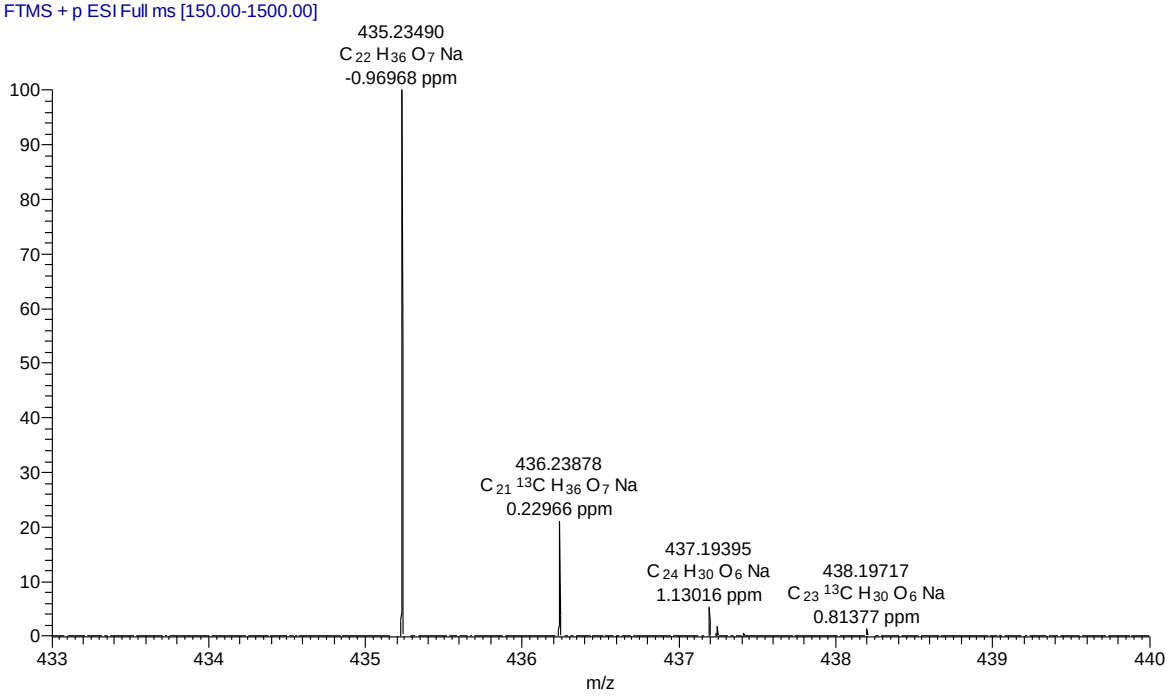

Figure S58. IR and HRMS spectra of **2**.

Acquisition Time (sec)	1.5903	***Date***	07 Mar 2014 13:39:24						
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Number of Transients	32	***Original Points Count***	16384	***Points Count***	65536	***Pulse Sequence***	zg30	***Solvent***	MeOD
Sweep Width (Hz)	10302.20	***Temperature (degree C)***	25.139						

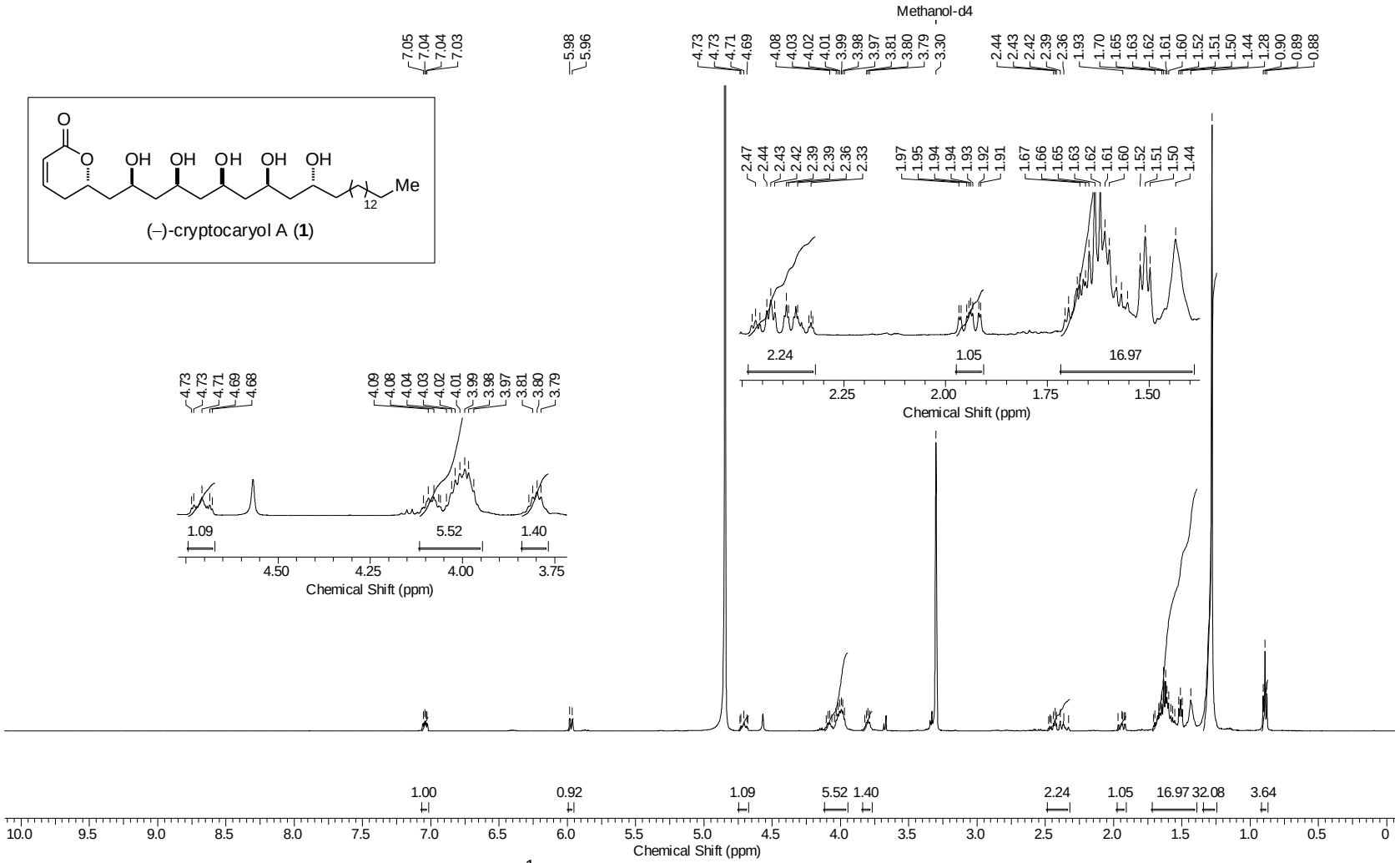


Figure S59. ^{1}H NMR spectrum of **1** (500 MHz; MeOD).

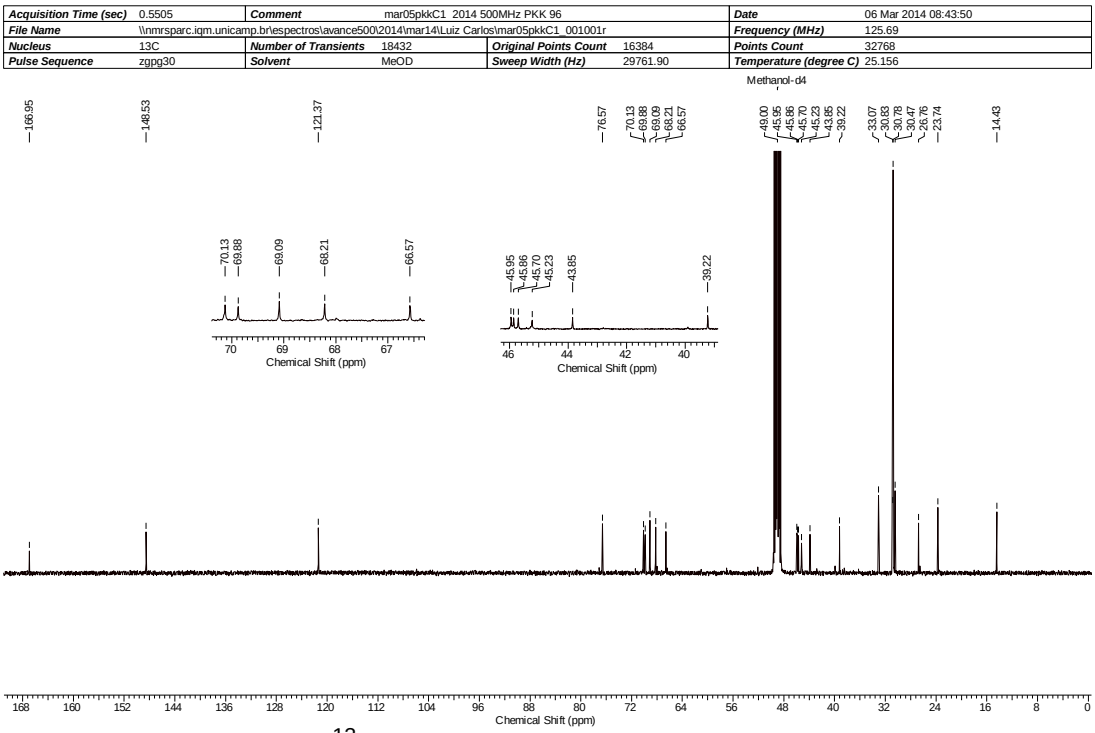


Figure S60. ^{13}C NMR spectrum of **1** (125 MHz; MeOD).

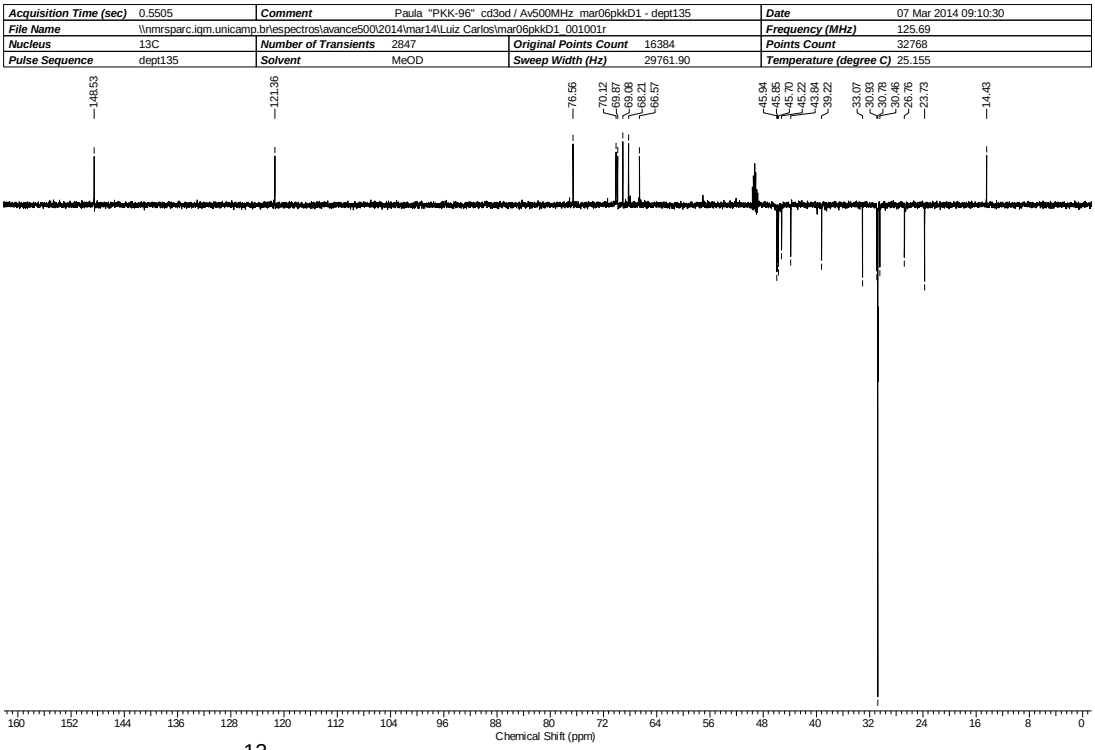
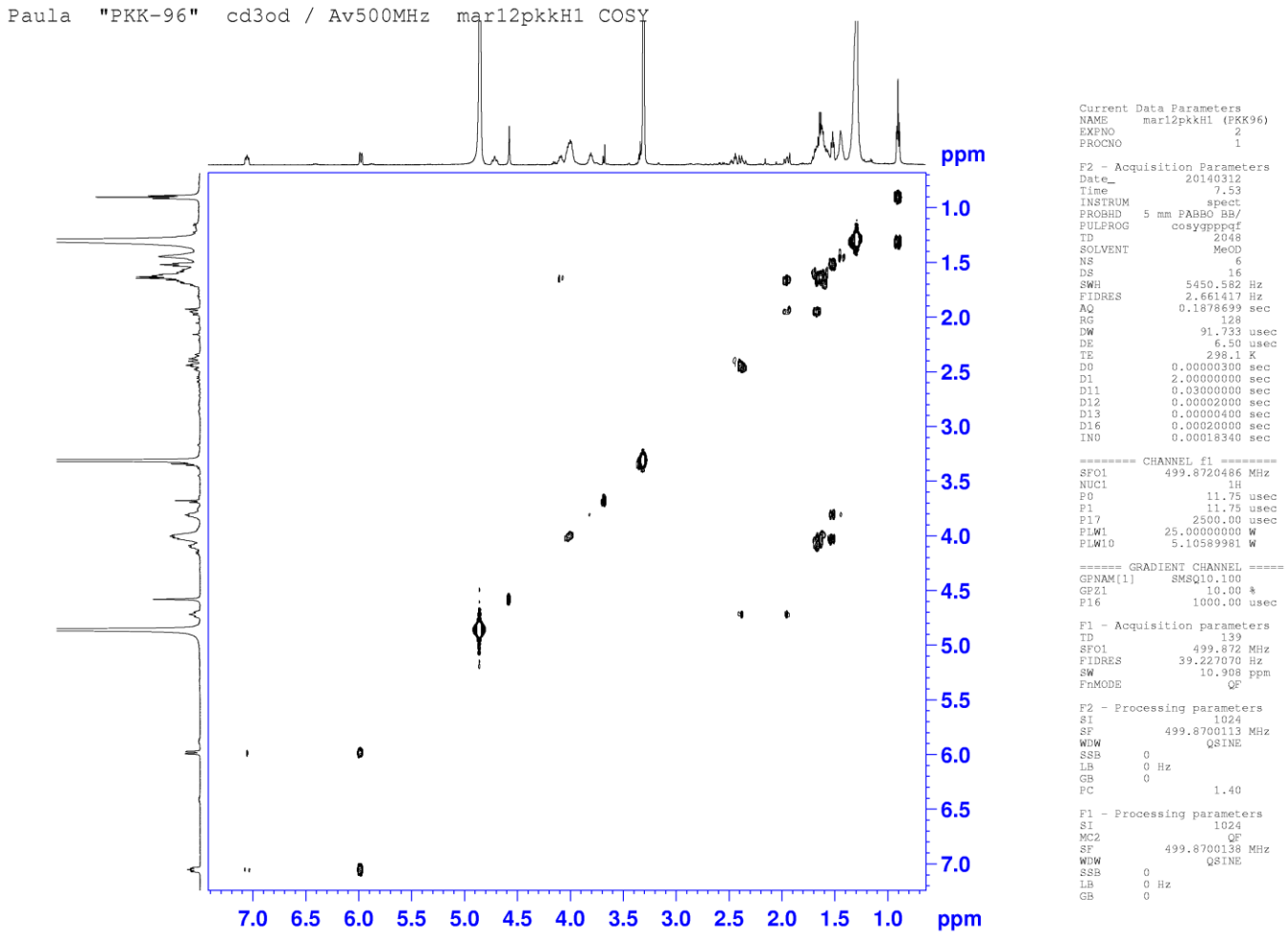


Figure S61. ^{13}C NMR spectrum (DEPT 135) of **1** (125 MHz; MeOD).

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PROCNO                 1

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PULPROG      cosygpppqf
TD                 2048
SOLVENT            MeOD
NS                    6
DS                   16
SWH           5450.582 Hz
FIDRES        2.661417 Hz
AQ            0.1878699 sec
RG                  128
DW               91.733 usec
DE                6.50 usec
TE              298.1 K
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D1            2.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00018340 sec

======== CHANNEL f1 ========
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NUC1               1H
P0                11.75 usec
P1                11.75 usec
P17             2500.00 usec
PLW1         25.00000000 W
PLW10         5.10589981 W

====== GRADIENT CHANNEL =====
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GPZ1             10.00 %
P16            1000.00 usec

F1 - Acquisition parameters
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FIDRES        39.227070 Hz
SW              10.908 ppm
FnMODE               QF

F2 - Processing parameters
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WDW                QSINE
SSB       0
LB        0 Hz
GB        0
PC                 1.40

F1 - Processing parameters
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MC2                  QF
SF           499.8700138 MHz
WDW                QSINE
SSB       0
LB        0 Hz
GB        0
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Figure S62. COSY contour map for **1**.

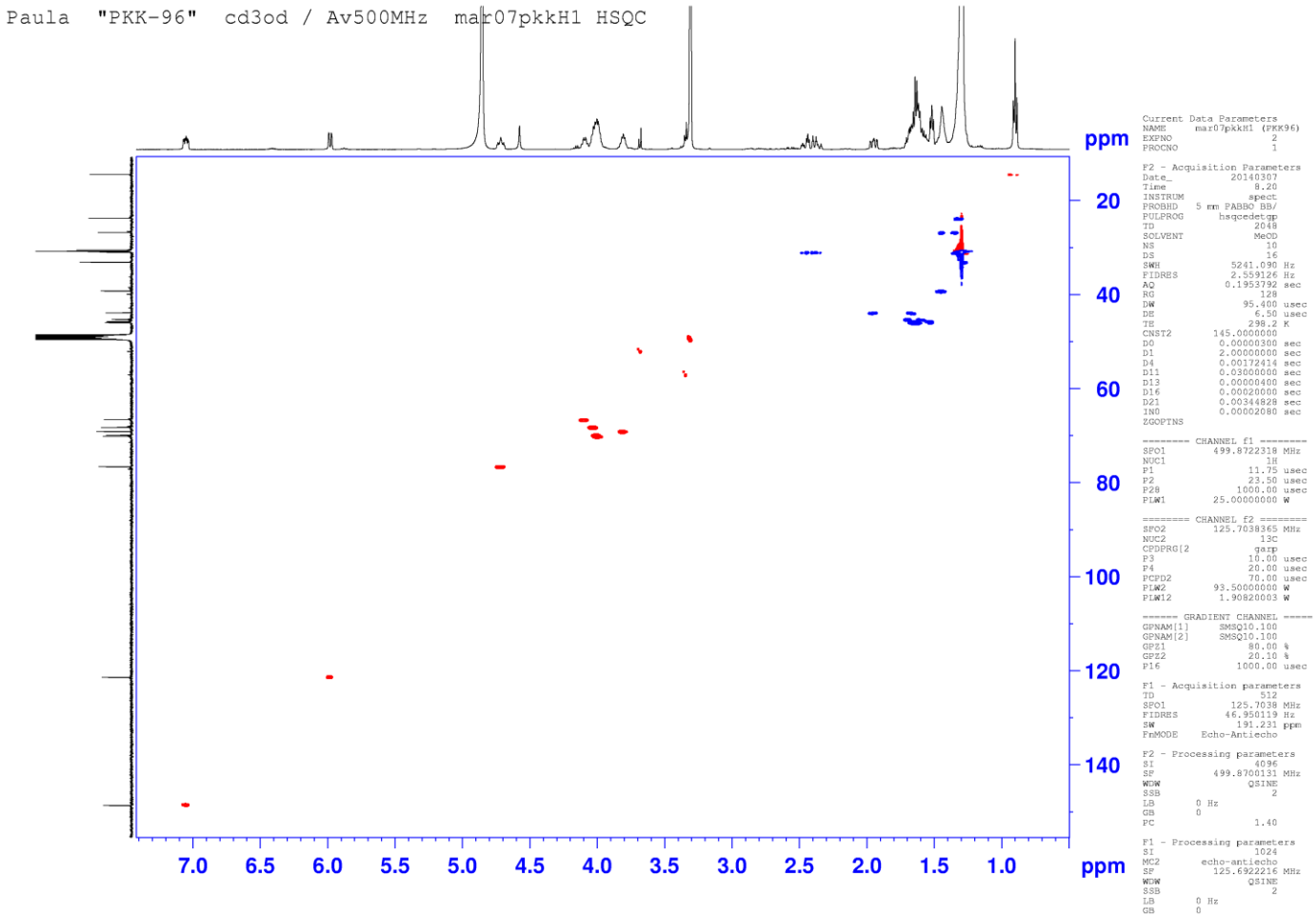


Figure S63. HSQC contour map for **1**.

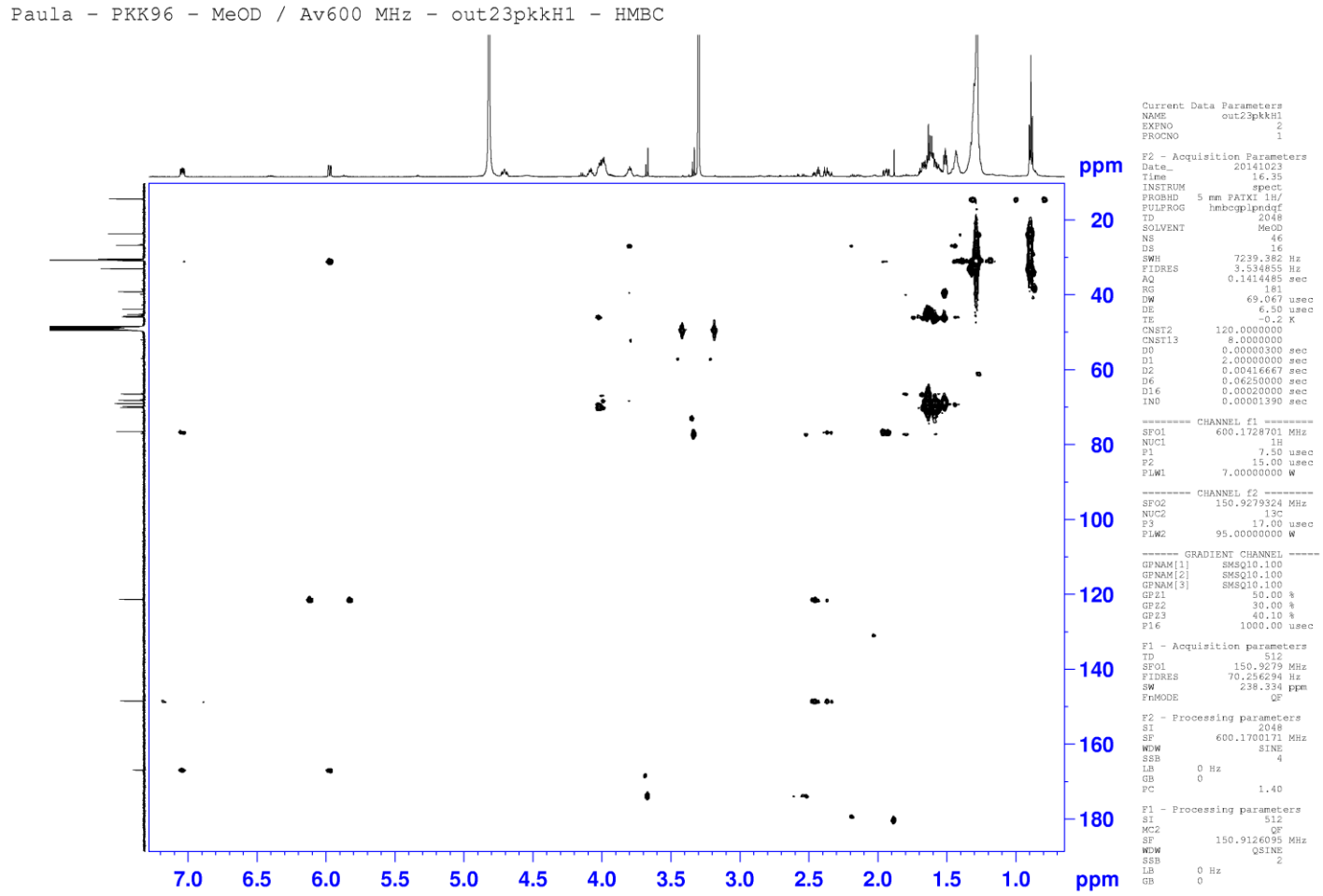
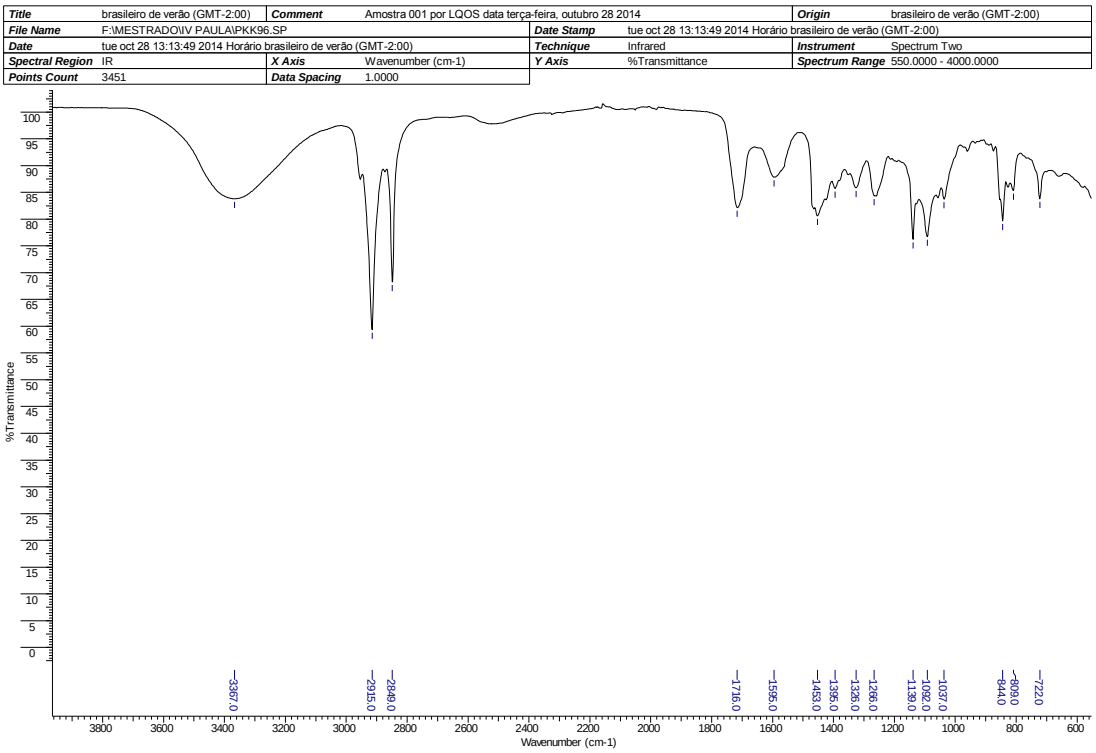


Figure S64. HMBC contour map for **1**.



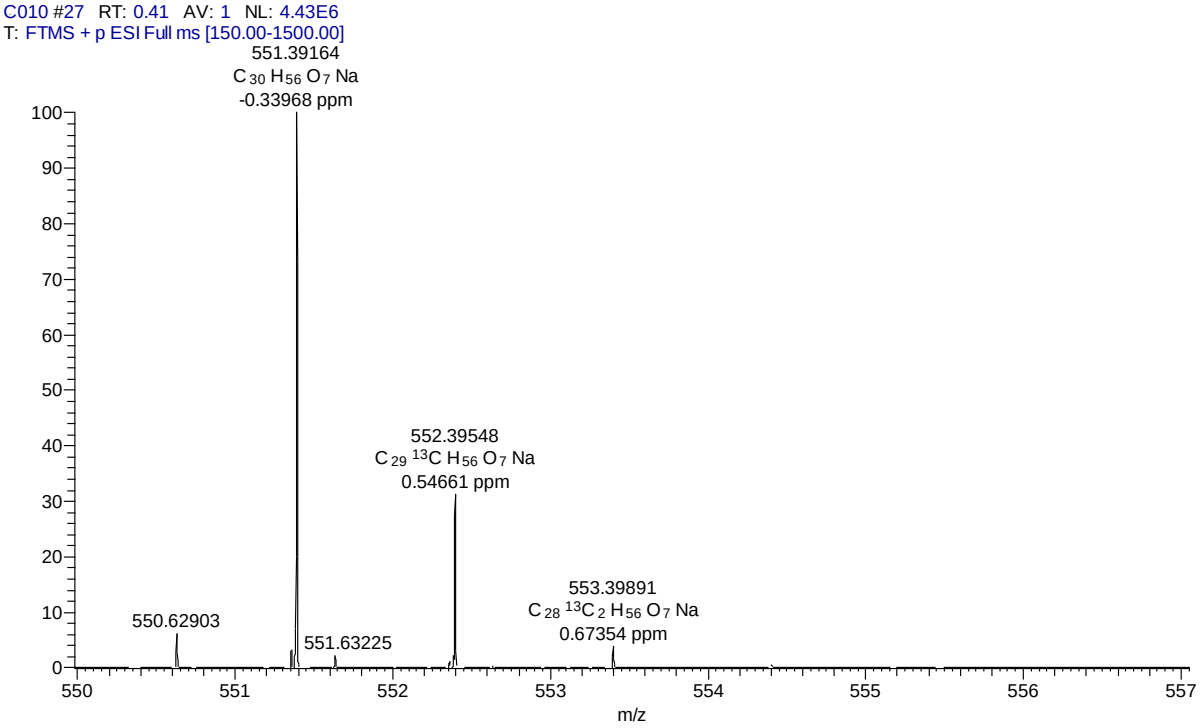


Figure S65. IR and HRMS spectra of **1**.

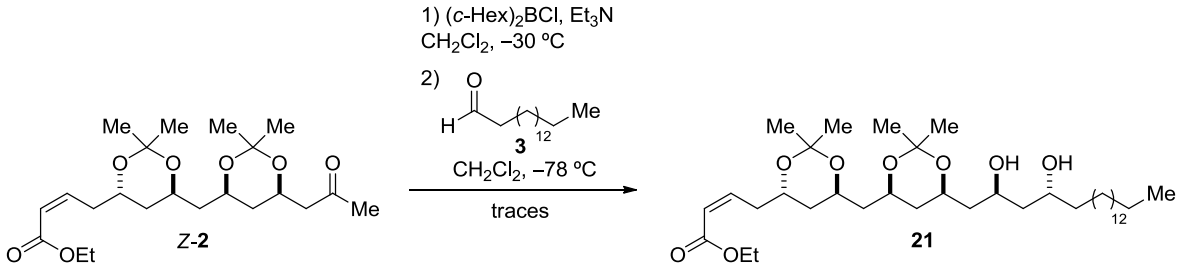
Table S1. ^{1}H and ^{13}C NMR chemical shifts for natural and synthetic cryptocaryol A.

Position	Natural Product			Dias Synthetic Product			O'Doherty Synthetic Product		
	δ ^{13}C	δ ^{1}H	multiplicity (*J* in Hz)	δ ^{13}C[c]	δ ^{1}H[a]	multiplicity (*J* in Hz)	δ ^{13}C	δ ^{1}H	multiplicity (*J* in Hz)
2	167.0			167.0			167.0		
3	121.4	5.97	dd (9.8, 1.9)	121.4	5.97	dd (9.6, 1.9)	121.4	5.97	dd (9.6, 2.5)
4	148.6	7.04	ddd (9.8, 6.0, 2.3)	148.5	7.05	ddd (9.6, 5.9, 2.4)	148.6	7.04	ddd (9.6, 6.0, 2.8)
5a	31.0	2.45	m	30.9	2.45	m	31.0	2.45	ddd (19.2, 5.2, 5.2)
5b		2.36	ddt (18.5, 11.8, 2.6)		2.36	ddt (18.5, 11.7, 2.5)		2.36	dddd (19.2, 11.6, 2.8, 2.8)
6	76.6	4.71	m	76.6	4.71	m	76.6	4.67-4.74	m
7a	43.9	1.94	ddd (14.5, 9.7, 2.3)	43.9	1.94	ddd (14.4, 9.9, 2.5)	43.9	1.94	ddd (14.8, 9.6, 2.8)
7b		1.67	m		1.66	m		1.55-1.71	m
8	66.6	4.08	m	66.6	4.08	m	66.6	4.09	(dddd, 8.8, 6.4, 6.4, 2.4)
9	46.0	1.68	m	46.0	1.63	m	46.0	1.55-1.71	m
10	69.9	3.97	m	69.9	4.00	m	69.9	3.96-4.04	m
11a	45.3	1.64	m	45.2	1.67	m	45.3	1.55-1.71	m
11b					1.60	m			
12	70.2	4.00	m	70.1	4.00	m	70.2	3.96-4.04	m
13	45.9	1.59	m	45.9	1.63	m	45.9	1.55-1.71	m
14	68.3	4.02	m	68.2	4.02	m	68.2	3.96-4.04	m
15	45.8	1.50	m	45.7	1.51	m	45.8	1.49-1.52	m
16	69.1	3.79	m	69.1	3.80	m	69.1	3.77-3.82	m
17	39.3	1.43	m	39.2	1.44	m	39.3	1.40-1.46	m
18a	26.8	1.32	m	26.8	1.43	m	26.8	1.25-1.32	m
18b					1,33	m			
19-28	30.5-31.0	1.27-1.29	br s	30.5-30.9	1.24-1.36	br s	30.5-31.0	1.25-1.32	br s
29	33.2	1.29	m	33.1	1.28	m	33.1	1.25-1.32	m
30	23.8	1.27	m	23.7	1.31	m	23.8	1.25-1.32	m
31	14.5	0.89	t (6.9)	14.4	0.89	t (7.0)	14.5	0.89	t (6.8)

[a] Assignment based on COSY, HSQC, and HMBC experiments.

Attempts to optimize de aldol reaction

To improve the yields in the last three steps of the (−)-cryptocaryol A synthesis, we first investigated the influence of the solvents in the aldol coupling. In the original procedure, Et_2O was used for enolization of methyl ketone *Z*-**2,** and a solution of hexadecanal in CH_2Cl_2 was added to the pre-formed enolate. We envisioned that using CH_2Cl_2 for both the enolization and aldehyde addition may improve the yield; however, only traces of the desired product were observed (Scheme S1).



Scheme S1.

Analysis of the byproducts from the aldol reaction in CH_2Cl_2 by ^1H NMR revealed a new signal at 6.77 ppm (doublet of triplets, J = 16.1, 7.1 Hz) corresponding to an *E* alkene. Unfortunately, the new peak corresponds to the isomerization product of compound *Z*-**2** under the reaction conditions (Figure S66).

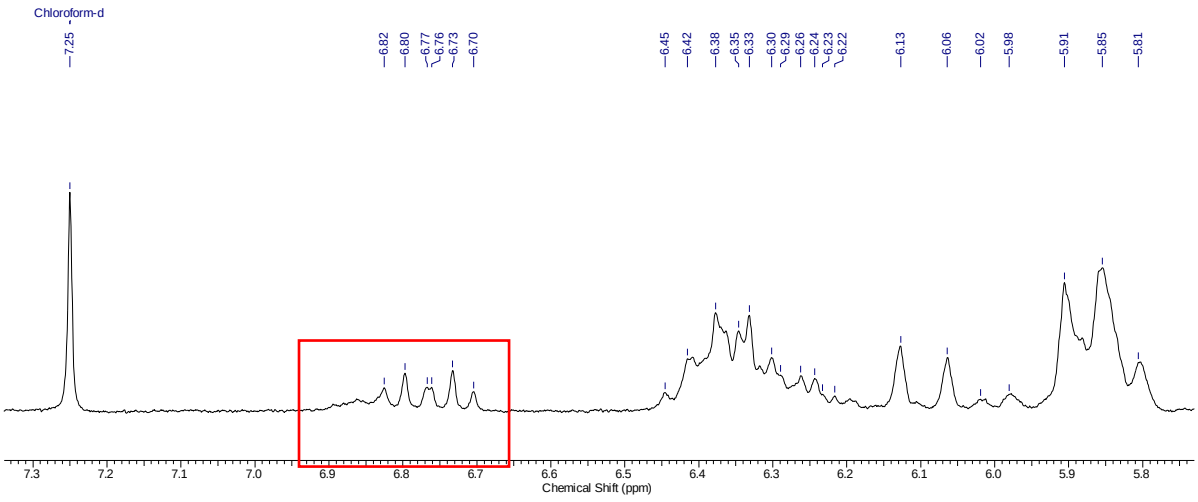
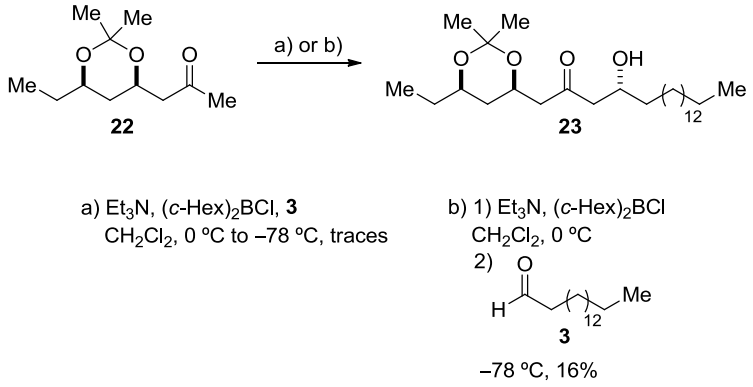


Figure S66.

We attributed the isomerization of methyl ketone *Z*-**2** to the complexation of the Lewis acid, (*c*-Hex)$_2$BCl, to the ester carbonyl. Thus, we began by investigating milder

enolization conditions to reduce the degradation of the starting material. Under the standard enolization conditions, (*c*-Hex)$_2$BCl is added to a solution of the methyl ketone at 0 ºC, followed by addition of Et_3N. After 30 minutes, the reaction mixture is cooled to −78 ºC, and a solution of the aldehyde is added. Therefore, we envisioned that reducing the enolization time or adding the Lewis acid to a mixture of the ketone and aldehyde in the aldol coupling may improve the yield. To investigate the effect of time and the order of addition of reagents, we used model methyl ketone **22**.

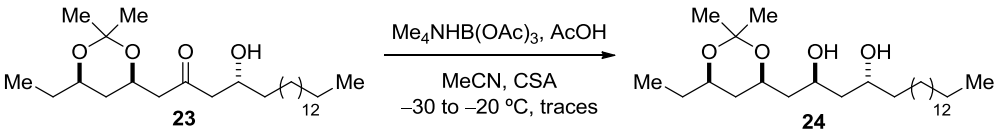
First, we performed the enolization of methyl ketone **22** in the presence of aldehyde **3**. However, only traces of the desired product were obtained. Next, (*c*-Hex)$_2$BCl was added to a solution of Et_3N and methyl ketone, and the enolate was allowed to form over 5 min before addition of the aldehyde. Under these conditions, the aldol adduct **23** was obtained in 16% yield (Scheme S2). However, the low yield in this reaction is inconsistent with the reaction progress observed on TLC. Therefore, we believe that the product degraded during purification on column chromatography.



Scheme S2.

To avoid potential degradation of aldol adduct **23**, the crude product was used in the subsequent step without purification by column chromatography. Therefore, the aldol reaction was accomplished according to Scheme S2b. After quenching the excess Lewis acid with MeOH, the volatiles were removed under reduced pressure, and the residue was diluted with CH_2Cl_2 and washed with H_2O to remove excess Et_3N•HCl formed during the reaction. The organic layer was concentrated and the crude product was submitted to a 1,3-*anti* reduction using the Evans method.[1] However, the crude aldol adduct **23** was insoluble in the solvent mixture (MeCN and AcOH) used for this reaction. Only a small amount of diol **24** was obtained and 10% of compound **23** was recovered (Scheme S3).

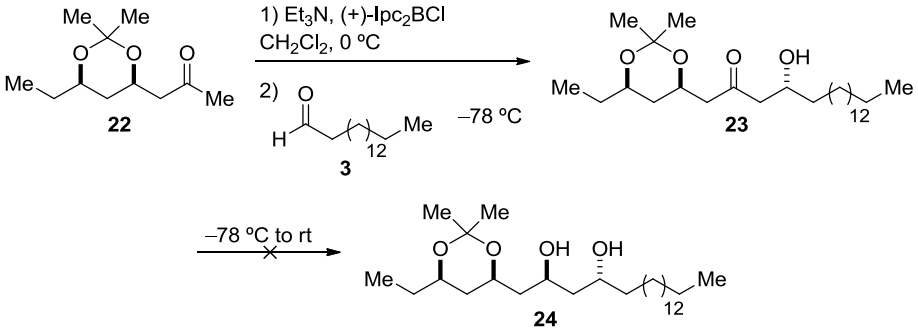
[1] a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.



Scheme S3.

Based on the poor solubility and yield for the 1,3-*anti* reduction, we decided to use an alternative method described by Dieckmann and Menche to effect the aldol reaction and subsequent reduction.[2] This method uses Ipc_2BCl as a Lewis acid in the initial aldol coupling between a methyl ketone and an aldehyde followed by a subsequent asymmetric reduction of the ketone carbonyl upon warming. The aldol reaction and tandem reduction affords products with 1,5-*anti* and 1,3-*syn* stereochemistry.

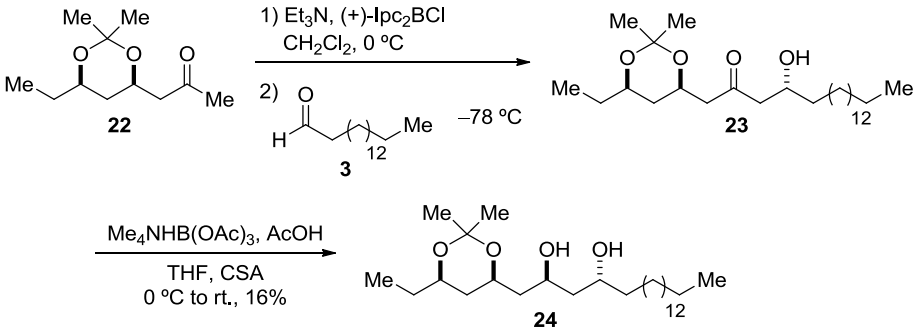
Application of the Dieckmann and Menche methodology to ketone **22** afforded the desired aldol product; however, no reduction of the ketone carbonyl was observed after 24 hours at room temperature by TLC (Scheme S4).



Scheme S4.

As an alternative, the aldol reaction was performed using (+)-Ipc_2BCl, and the corresponding product was reduced using the Evans method with THF as solvent. However, the solubility of compound **23** in THF was low and only 16% of diol **24** was obtained (Scheme S5).

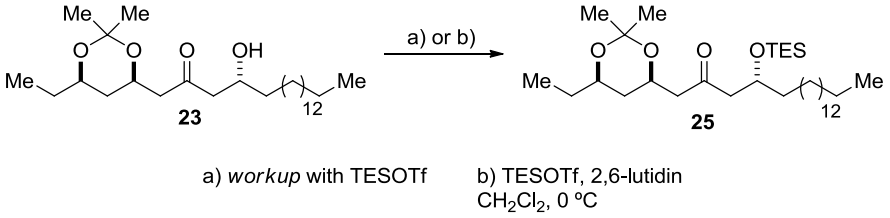
[2] Dieckmann, M.; Menche, D. *Org.Lett.* **2013**, *15*, 228.



Scheme S5.

Since optimization of both the aldol coupling between **22** and **3** and the reduction of **23** were difficult, we decided to protect the hydroxyl of **23** as the TES ether with TESOTf to improve its solubility for a stereoselective carbonyl reduction. Therefore, the aldol reaction involving methyl ketone **22** and aldehyde **3** was quenched by addition of TESOTf at –78 ºC, and gradually warmed to room temperature (Scheme S6a). However, the TLC of aldol reaction after the addition of TESOTf remained the same and the desired silyl ether was not isolated.

We envisioned that the silyl protection failed because the Lewis acid was still coordinated to the secondary alcohol. Therefore, the aldol reaction was accomplished again, and after the reaction was complete the excess Lewis acid was quenched with MeOH and the reaction medium was washed with H_2O. The crude product was then treated with TESOTf and 2,6-lutidine, but only a complex mixture of byproducts was observed (Scheme S6b). [3]



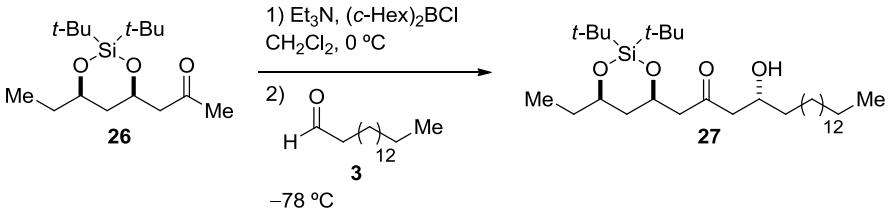
Scheme S6.

Finally, we decided to investigate the influence of eluents used during purification of the aldol adduct by column chromatography. Model substrate **26** was submitted twice to the aldol reaction conditions shown in Scheme S7. Purification of **27** was first performed by loading the crude product on the column with CH_2Cl_2, followed by using a mixture of

[3] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4ª ed.; John Wiley & Sons; Nova York, 2007.

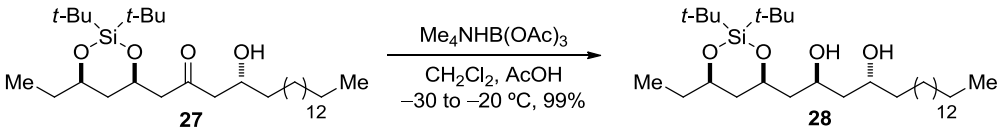
hexane and ethyl acetate as eluent. With these conditions, only traces of the desired product were isolated.

For the second purification, the crude product was loaded on the column with CH_2Cl_2 and this solvent was also used as eluent. In this case, the aldol adduct **27** was obtained in 44% yield, which is a superior yield to those observed for reactions involving aldehyde **3**.



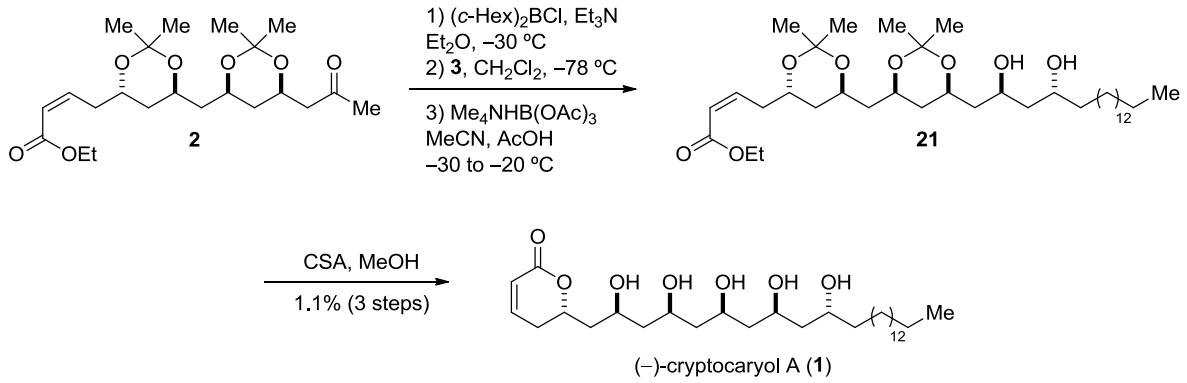
Scheme S7.

The reduction step was then optimized by substituting MeCN, used in the Evans methodology, for CH_2Cl_2, which can solubilize both the starting material and reducing agent. Reaction of aldol adduct **27** with $Me_4NHB(OAc)_3$ in CH_2Cl_2 and AcOH afforded diol **28** in 99% yield, which demonstrates that CH_2Cl_2 is the ideal solvent for substrate **27** (Scheme S8). Furthermore, aldol adduct **27** could be reduced to diol **28** under the optimized conditions, albeit in poor yield.



Scheme S8.

With the optimized conditions for the model substrate in hand, we next applied them to the actual substrate. Since the solvent mixture did not influence the yields in the aldol reaction, Et_2O was used for enolization of methyl ketone **2** (Scheme S8). The aldol adduct was then purified with a mixture of CH_2Cl_2:AcOEt (9:1) as eluent. Subsequent reduction of the aldol adduct under the Evans conditions using CH_2Cl_2 afforded compound **21**. The crude product was partially purified by column chromatography and then treated with CSA in MeOH to give (−)-cryptocaryol A in 1.1% yield over 3 steps (Scheme S9).


1) (c-Hex)2BCl, Et3N
Et2O, –30 ºC
2) 3, CH2Cl2, –78 ºC
3) Me4NHB(OAc)3
MeCN, AcOH
–30 to –20 ºC
2
21
CSA, MeOH
1.1% (3 steps)
(–)-cryptocaryol A (1)

Scheme S9.