

## Supporting Information

### **Substrate geometry controls the cyclization cascade in Multiproduct terpene synthases from *Zea Mays***

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*<sup>1</sup>H, <sup>13</sup>C spectra of the synthetic compounds*

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*<sup>31</sup>P NMR spectra of the synthetic compounds*

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IR spectra of the synthetic compounds

[2,2- <sup>2</sup> H <sub>2</sub> ]-Trimethylsilylacetic acid ( <b>4</b> )	S22
[1,1,1,3,3- <sup>2</sup> H <sub>5</sub> ]-6-Methyl-hept-5-en-2-one ( <b>3b</b> )	S24
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**Product distribution of main monoterpenes from incubations of deuterated GDP with TPS4-B73 and TPS5-Delprim from maize (*Zea mays*)**

enzyme	product distribution <sup>a, b</sup> ng/h (% composition)	substrate				
		<i>E</i> -GDP <sup>c</sup>	<i>E</i> -(1D)-GDP <b>7a</b>	<i>Z</i> -(1D)-GDP <b>8a</b>	<i>E</i> -(6D)-GDP <b>7b</b>	<i>Z</i> -(6D)-GDP <b>8b</b>
<b>TPS4</b>	$\alpha$ -Thujene (M <sub>1</sub> )*	15.4 ± 0.5 (3.3)	15.6 ± 0.2 (3.1)	20.8 ± 0.8 (3.3)	5.0 ± 0.0 (1.2)	5.7 ± 0.1 (1.0)
	Sabinene (M <sub>2</sub> )*	39.7 ± 1.2 (8.4)	41.8 ± 0.3 (8.4)	63.1 ± 0.6 (9.9)	18.0 ± 0.9 (4.2)	31.4 ± 0.8 (5.3)
	$\beta$ -Myrcene (M <sub>3</sub> )	42.6 ± 2.0 (9.1)	42.9 ± 0.5 (8.6)	-	26.9 ± 0.6 (6.4)	-
	(S)-(-)-Limonene (M <sub>4</sub> )	101.1 ± 3.5 (21.5)	100.9 ± 1.6 (20.3)	245.9 ± 3.4 (38.6)	95.2 ± 2.1 (22.5)	236.3 ± 4.3 (39.6)
	Sabinene hydrate (M <sub>5</sub> )**	26.7 ± 1.2 (5.7)	31.2 ± 1.0 (6.3)	38.8 ± 1.3 (6.1)	39.6 ± 0.7 (9.3)	62.6 ± 1.2 (10.5)
	$\alpha$ -Terpinolene (M <sub>6</sub> )	21.4 ± 0.4 (4.5)	22.4 ± 0.2 (4.5)	91.9 ± 1.4 (14.4)	21.7 ± 0.5 (5.1)	89.9 ± 2.3 (15.1)
	Linalool (M <sub>7</sub> )*	112.1 ± 4.2 (23.9)	128.5 ± 3.6 (25.9)	17.8 ± 1.0 (2.8)	115.8 ± 2.1 (27.3)	27.9 ± 0.6 (4.7)
	$\alpha$ -Terpineol (M <sub>8</sub> )*	30.6 ± 1.7 (6.5)	34.9 ± 0.8 (7.0)	78.6 ± 3.8 (12.3)	29.7 ± 0.3 (7.0)	76.2 ± 1.2 (12.8)
	Geraniol (M <sub>9</sub> )	79.7 ± 3.3 (17.0)	78.7 ± 2.7 (15.8)	80.7 ± 3.0 (12.6)	71.3 ± 1.8 (16.8)	66.0 ± 0.9 (11.1)

<sup>a</sup> Product distribution was determined by GC-FID analysis. <sup>b</sup> Average of three independent replicates. <sup>c</sup> GDP denotes the geranyl diphosphate. \* Stereoisomeric pairs chromatographically not resolved. \*\* Compound identified by mass spectra alone.

Enzyme	product distribution <sup>a, b</sup> ng/h (% composition)	substrate				
		<i>E</i> -GDP <sup>c</sup>	<i>E</i> -(1D)-GDP <b>7a</b>	<i>Z</i> -(1D)-GDP <b>8a</b>	<i>E</i> -(6D)-GDP <b>7b</b>	<i>Z</i> -(6D)-GDP <b>8b</b>
<b>TPS5</b>	$\alpha$ -Thujene (M <sub>1</sub> )*	67.0 ± 4.5 (2.5)	66.3 ± 2.4 (2.4)	166.9 ± 3.1 (5.0)	18.4 ± 1.1 (0.8)	46.4 ± 1.1 (1.5)
	Sabinene (M <sub>2</sub> )*	303.9 ± 4.4 (11.2)	294.8 ± 3.5 (10.7)	644.1 ± 8.3 (19.2)	127.9 ± 1.5 (5.4)	316.7 ± 12.4 (10.2)
	$\beta$ -Myrcene (M <sub>3</sub> )	534.1 ± 14.6 (19.6)	498.0 ± 11.1 (18.0)	11.9 ± 1.6 (0.3)	348.1 ± 2.6 (14.8)	10.2 ± 2.9 (0.3)
	(S)-(-)-Limonene (M <sub>4</sub> )	570.0 ± 10.2 (20.9)	546.5 ± 6.3 (19.8)	1404.0 ± 12.1 (42.0)	500.4 ± 9.9 (21.3)	1383.4 ± 33.2 (44.6)
	Sabinene hydrate (M <sub>5</sub> )**	198.3 ± 13.2 (7.3)	212.6 ± 2.3 (7.7)	452.0 ± 4.7 (13.5)	304.0 ± 10.2 (12.9)	648.9 ± 48.0 (20.9)
	$\alpha$ -Terpinolene (M <sub>6</sub> )	92.6 ± 2.8 (3.4)	89.0 ± 0.2 (3.2)	194.0 ± 4.7 (5.8)	86.7 ± 2.0 (3.7)	208.8 ± 8.0 (6.7)
	Linalool (M <sub>7</sub> )*	317.0 ± 23.2 (11.6)	339.4 ± 4.7 (12.3)	137.6 ± 18.5 (4.1)	332.2 ± 17.3 (14.1)	189.9 ± 15.4 (6.1)
	$\alpha$ -Terpineol (M <sub>8</sub> )*	140.8 ± 11.5 (5.2)	157.9 ± 4.6 (5.7)	322.1 ± 34.73 (9.6)	135.3 ± 7.0 (5.8)	286.1 ± 20.2 (9.2)
	Geraniol (M <sub>9</sub> )	500.0 ± 47.3 (18.4)	559.2 ± 3.5 (20.2)	12.9 ± 4.1 (0.4)	495.8 ± 34.8 (21.1)	11.2 ± 0.4 (0.3)

<sup>a</sup> Product distribution was determined by GC-FID analysis. <sup>b</sup> Average of three independent replicates. <sup>c</sup> GDP denotes the geranyl diphosphate. \* Stereoisomeric pairs chromatographically not resolved. \*\* Compound identified by mass spectra alone.

**Product distribution of main sesquiterpenes from incubations of deuterated FDP with  
TPS4-B73 from maize (*Zea mays*)**

enzyme	product distribution <sup>a, b</sup> ng/h (% composition)	substrate				
		<i>E</i> -FDP <sup>c</sup>	<i>E,E</i> -(1D)-FDP <b>7c</b>	<i>Z,E</i> -(1D)-FDP <b>8c</b>	<i>E,E</i> -(6D)-FDP <b>7d</b>	<i>Z,E</i> -(6D)-FDP <b>8d</b>
TPS4	7- <i>epi</i> -Sesquithujene (S <sub>1</sub> )	568.8 ± 25.4 (18.5)	713.2 ± 75.9 (20.0)	2395.1 ± 55.3 (29.3)	349.4 ± 19.4 (12.1)	1552.2 ± 30.6 (16.8)
	Sesquithujene (S <sub>2</sub> )	133.3 ± 6.0 (4.3)	165.4 ± 17.3 (4.6)	635.7 ± 14.5 (7.8)	55.9 ± 3.0 (1.9)	278.4 ± 5.0 (3.0)
	( <i>Z</i> )- $\alpha$ -Bergamotene (S <sub>3</sub> )	30.5 ± 1.5 (1.0)	40.2 ± 4.0 (1.1)	66.3 ± 1.4 (0.8)	21.3 ± 1.1 (0.7)	42.2 ± 0.7 (0.4)
	( <i>E</i> )- $\alpha$ -Bergamotene (S <sub>4</sub> )	47.8 ± 2.0 (1.5)	65.4 ± 7.1 (1.8)	203.8 ± 4.7 (2.5)	16.7 ± 0.8 (0.6)	80.8 ± 1.6 (0.9)
	Sesquisabinene A (S <sub>5</sub> )	72.9 ± 2.9 (2.4)	91.0 ± 8.0 (2.5)	328.3 ± 6.9 (4.0)	57.5 ± 3.0 (2.0)	246.7 ± 4.0 (2.7)
	Sesquisabinene B (S <sub>6</sub> )	29.9 ± 1.2 (1.0)	36.5 ± 2.9 (1.0)	175.7 ± 3.7 (2.1)	26.3 ± 1.3 (0.9)	144.2 ± 2.3 (1.6)
	( <i>E</i> )- $\beta$ -Farnesene (S <sub>7</sub> )	88.2 ± 3.4 (2.9)	112.5 ± 11.2 (3.1)	-	82.8 ± 4.2 (2.9)	-
	$\gamma$ -Curcumene (S <sub>8</sub> )*	9.4 ± 0.3 (0.3)	11.0 ± 1.0 (0.3)	68.3 ± 3.4 (0.8)	25.2 ± 1.5 (0.9)	134.6 ± 2.0 (1.4)
	Zingiberene (S <sub>9</sub> )*	27.6 ± 2.0 (0.9)	34.3 ± 4.5 (1.0)	122.6 ± 2.7 (1.5)	25.4 ± 1.3 (0.9)	105.3 ± 2.3 (1.1)
	( <i>S</i> )- $\beta$ -Bisabolene (S <sub>10</sub> )	584.4 ± 23.0 (19.1)	737.3 ± 74.2 (20.7)	1983.6 ± 42.8 (24.3)	573.1 ± 31.2 (19.9)	2053.2 ± 41.1 (22.2)
	$\beta$ -Curcumene (S <sub>11</sub> )*	19.7 ± 0.6 (0.6)	23.0 ± 1.9 (0.6)	98.5 ± 5.0 (1.2)	68.5 ± 3.6 (2.4)	299.9 ± 4.9 (3.2)
	( <i>E</i> )- $\gamma$ -Bisabolene (S <sub>12</sub> )	45.0 ± 1.6 (1.5)	56.1 ± 5.5 (1.6)	152.1 ± 3.3 (1.9)	44.2 ± 2.4 (1.5)	159.9 ± 3.1 (1.7)
	7- <i>epi</i> -Sesquithujene hydrate (S <sub>13</sub> )**	174.0 ± 4.8 (5.7)	182.3 ± 0.9 (5.1)	809.6 ± 28.3 (9.9)	363.5 ± 20.9 (12.6)	1873.0 ± 22.9 (20.3)
	Sesquithujene hydrate (S <sub>14</sub> )**	116.7 ± 3.6 (3.8)	116.1 ± 0.7 (3.2)	505.9 ± 19.1 (6.2)	200.8 ± 11.8 (7.0)	1093.8 ± 25.3 (11.8)
	(3 <i>R</i> )-(E)-Nerolidol (S <sub>15</sub> )	458.3 ± 13.8 (14.9)	481.4 ± 10.6 (13.5)	-	344.1 ± 21.1 (11.9)	-
	Unknown (A)***	525.6 ± 14.7 (17.1)	550.2 ± 2.8 (15.4)	7.1 ± 1.4 (0.1)	411.3 ± 23.6 (14.3)	8.12 ± 0.7 (0.1)
	Unknown (B)***	29.8 ± 0.9 (1.0)	30.9 ± 0.1 (0.9)	148.9 ± 6.7 (1.8)	69.8 ± 4.1 (2.4)	393.3 ± 6.9 (4.2)
	Unknown (C)***	51.7 ± 2.4 (1.7)	51.6 ± 0.7 (1.4)	229.2 ± 10.2 (2.8)	80.8 ± 4.7 (2.0)	487.4 ± 8.5 (5.3)

<sup>a</sup> Product distribution was determined by GC-FID analysis. <sup>b</sup> Average of three independent replicates. <sup>c</sup> GDP denotes the geranyl diphosphate. \* Absolute configuration of the stereoisomeric pairs uncertain. \*\* Hypothetic structure. Compounds identified by mass spectra alone. \*\*\* Unknown oxygenated cyclic sesquiterpenes.

**Product distribution of main sesquiterpenes from incubations of deuterated FDP with**

**TPS5-Delprim from maize (*Zea mays*)**

enzyme	product distribution <sup>a, b</sup> ng/h (% composition)	substrate				
		<i>E</i> -FDP <sup>c</sup>	<i>E,E</i> -(1D)-FDP <b>7c</b>	<i>Z,E</i> -(1D)-FDP <b>8c</b>	<i>E,E</i> -(6D)-FDP <b>7d</b>	<i>Z,E</i> -(6D)-FDP <b>8d</b>
TPS5	<i>7-epi</i> -Sesquithujene (S <sub>1</sub> )	196.6 ± 2.0 (2.0)	200.4 ± 2.1 (2.0)	1035.7 ± 14.6 (3.9)	132.0 ± 5.1 (1.2)	633.0 ± 13.7 (2.4)
	Sesquithujene (S <sub>2</sub> )	2854.3 ± 28.8 (29.3)	2967.0 ± 35.2 (29.2)	8442 ± 129.9 (32.3)	1265.8 ± 32.8 (11.6)	3497.7 ± 95.7 (13.2)
	( <i>Z</i> )- $\alpha$ -Bergamotene (S <sub>3</sub> )	245.4 ± 2.4 (2.5)	268.4 ± 2.7 (2.6)	484.0 ± 7.1 (1.8)	134.8 ± 2.8 (1.2)	209.8 ± 5.2 (0.8)
	( <i>E</i> )- $\alpha$ -Bergamotene (S <sub>4</sub> )	33.5 ± 0.4 (0.3)	36.1 ± 0.5 (0.3)	360.7 ± 5.9 (1.4)	23.6 ± 2.0 (0.2)	274.4 ± 9.0 (1.0)
	Sesquisabinene A (S <sub>5</sub> )	31.8 ± 0.4 (0.3)	30.5 ± 0.4 (0.3)	187.1 ± 2.8 (0.7)	28.1 ± 1.5 (0.2)	141.8 ± 5.4 (0.5)
	Sesquisabinene B (S <sub>6</sub> )	526.9 ± 5.1 (5.4)	557.5 ± 7.0 (5.5)	1545.5 ± 27.0 (5.9)	438.0 ± 8.1 (4.0)	1096.1 ± 46.9 (4.1)
	( <i>E</i> )- $\beta$ -Farnesene (S <sub>7</sub> )	299.7 ± 22.1 (3.1)	330.5 ± 3.2 (3.2)	18.4 ± 1.8 (0.1)	321.1 ± 5.3 (2.9)	-
	$\gamma$ -Curcumene (S <sub>8</sub> )*	60.3 ± 1.0 (0.6)	63.44 ± 1.5 (0.6)	184.2 ± 2.7 (0.7)	139.0 ± 0.2 (1.3)	367.6 ± 16.5 (1.4)
	Zingiberene (S <sub>9</sub> )*	60.5 ± 0.7 (0.6)	60.4 ± 0.6 (0.6)	219.5 ± 4.1 (0.8)	66.3 ± 1.7 (0.6)	219.9 ± 10.8 (0.8)
	( <i>S</i> )- $\beta$ -Bisabolene (S <sub>10</sub> )	2223.7 ± 19.8 (22.8)	2363.6 ± 25.8 (23.3)	8746.3 ± 165 (33.4)	2352.5 ± 91.4 (21.6)	8172.4 ± 463 (30.9)
	$\beta$ -Curcumene (S <sub>11</sub> )*	82.6 ± 1.5 (0.8)	90.0 ± 2.0 (0.9)	224.9 ± 2.8 (0.8)	201.9 ± 0.6 (1.8)	510.1 ± 25.2 (1.9)
	( <i>E</i> )- $\gamma$ -Bisabolene (S <sub>12</sub> )	87.4 ± 0.9 (0.9)	91.8 ± 0.9 (0.9)	314.8 ± 6.1 (1.2)	98.4 ± 3.3 (0.9)	312.5 ± 18.9 (1.2)
	<i>7-epi</i> -Sesquithujene hydrate (S <sub>13</sub> )**	58.8 ± 0.8 (0.6)	60.4 ± 1.4 (0.6)	276.3 ± 5.1 (1.0)	138.1 ± 2.6 (1.3)	575.3 ± 32.8 (2.2)
	Sesquithujene hydrate (S <sub>14</sub> )**	1185.0 ± 13.0 (12.2)	1218.1 ± 15.9 (12.0)	2104.2 ± 304 (8.0)	2578.4 ± 45.3 (23.6)	5394.2 ± 299 (20.4)
	(3 <i>R</i> )-( <i>E</i> )-Nerolidol (S <sub>15</sub> )	596.8 ± 3.9 (6.1)	592.0 ± 5.1 (5.8)	-	566.5 ± 22.1 (5.2)	-
	Unknown (A)***	230.9 ± 2.4 (2.4)	221.0 ± 2.6 (2.2)	-	206.1 ± 6.0 (0.2)	3.0 ± 3.0 (0)
Unknown (B)***	12.5 ± 0.2 (0.1)	10.8 ± 0.9 (0.1)	69.3 ± 1.0 (0.3)	26.4 ± 0.7 (0.2)	154.0 ± 7.9 (0.6)	
Unknown (C)***	896.8 ± 9.2 (9.2)	918.6 ± 9.4 (9.0)	1792.2 ± 31.1 (6.8)	2104.1 ± 41.2 (19.3)	4449.7 ± 225 (16.8)	

<sup>a</sup> Product distribution was determined by GC-FID analysis. <sup>b</sup> Average of three independent replicates. <sup>c</sup> GDP denotes the geranyl diphosphate. \* Absolute configuration of the stereoisomeric pairs uncertain. \*\* Hypothetic structure. Compounds identified by mass spectra alone. \*\*\* Unknown oxygenated cyclic sesquiterpenes.

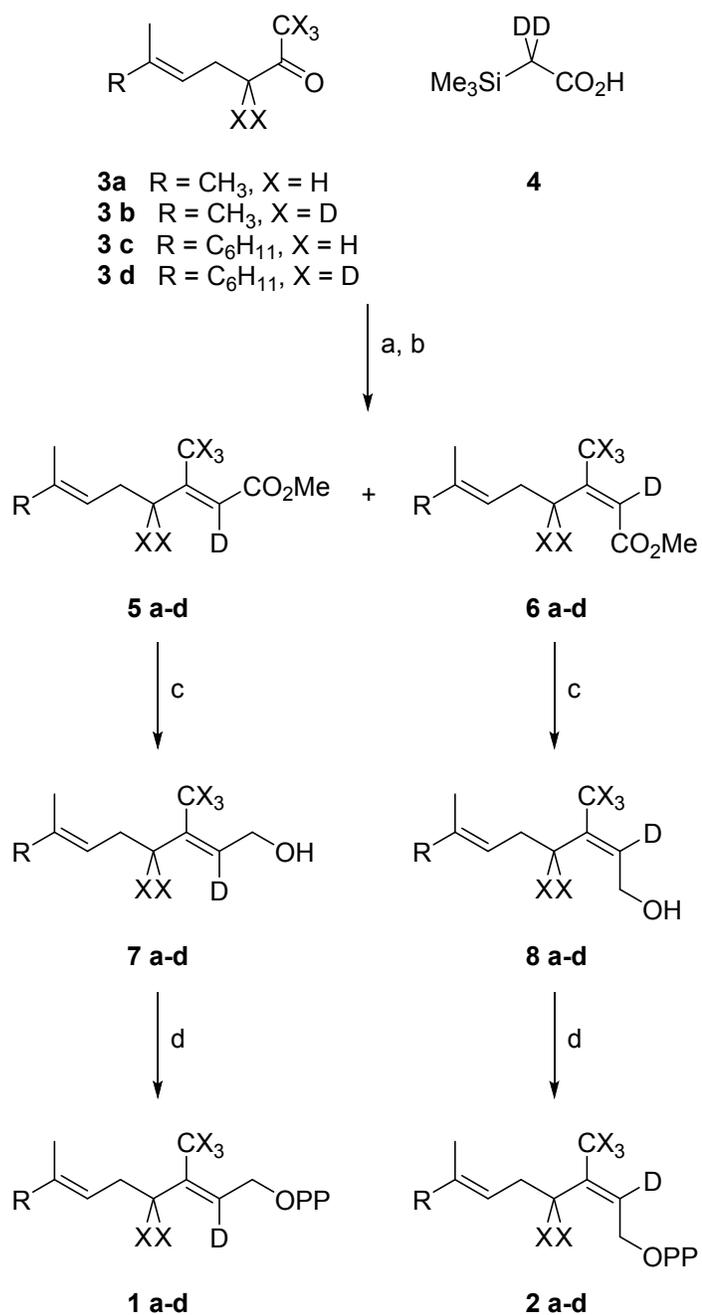
## Oxygenated cyclic volatiles approximation

To estimate the weight of this approximation, quantitative kinetic measurements were carried out. Since TPS4-B73 and TPS5-*Delprim* exhibit similar basic features, only deuterium isotope effects on the catalytic activity of TPS4 were evaluated using the noncompetitive method. Both unlabeled (2*E*,6*E*)-FDP and (2*E*,6*E*)-[<sup>2</sup>H<sub>6</sub>]-FDP **1d** substrates were used in two independent enzyme assays. Standard enzyme assays were performed in triplicate with aliquots of the same enzyme extracts under saturated substrate conditions. A decrease of 13 % (relative to the reference substrate) of the maximal rate for sesquiterpene formation was observed when (2*E*,6*E*)-[<sup>2</sup>H<sub>6</sub>]-FDP **1d** was incubated with TPS4, while similar  $K_m$  were obtained for both substrates. Since the kinetic experiments were performed using the same enzyme extract, the total enzyme concentration  $[E_T]$  was identical for both assays. Therefore, the turnover number ( $k_{cat}$ ) of the enzyme, usually defined as the ratio of  $V_{max}/[E_T]$ , can be approximated to  $V_{max}$ . The apparent total rate isotope effect  $k_H/k_D$ , determined from the maximal rates, equals 1.15. As discussed before, similar results were obtained when the oxygenated cyclic volatiles were not considered (19 % decrease in the volatile production corresponding to a  $k_H/k_D = 1.23$ ) and justify the approximation made above.

## Experimental Section

**General Methods.** Reactions were performed under Ar. Solvents were dried according to standard procedures.  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$  NMR: Bruker AV 400 spectrometer (Bruker, D-76287 Rheinstetten/Karlsruhe, Germany). Chemical shifts of  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$  NMR are given in ppm ( $\delta$ ) based on solvent picks.  $\text{CDCl}_3$ : 7.27 (1H NMR) and 77.4 ppm ( $^{13}\text{C}$  NMR).  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ : 4.79 ( $^1\text{H}$  NMR);  $^{13}\text{C}$  NMR and  $^{31}\text{P}$  NMR were referenced to external standard 3-(trimethylsilyl)-propionic acid- $\text{d}_4$  sodium salt (TSP; 3 % in  $\text{D}_2\text{O}$ ) and phosphoric acid ( $\text{H}_3\text{PO}_4$ , 10 % in  $\text{D}_2\text{O}$ ), respectively. IR: Bruker Equinox 55 FTIR spectrophotometer. GC-MS: Trace MS, 2000 Series (Thermoquest, D-63329 Egelsbach, Germany) equipped with an Alltech DB5 (15 m  $\varnothing$  0.25 mm, 0.25  $\mu\text{m}$ ); helium served as carrier gas. Molecular composition of prepared compounds were determined by ESI-MS using a Micromass Quattro II (Waters, Micromass, Manchester, UK) tandem quadrupole mass spectrometer (geometry quadrupole-hexapole-quadrupole) equipped with an electrospray (ESI) source. High resolution ESI-MS (HR-EI-MS) were recorded at resolution ca 2500. High-resolution MS (EI) data were obtained using a MasSpec 2 instrument (Micromass, UK) in positive ion mode using 70 eV ionization energy. GC-HR-MS: Analyses were performed with a Hewlett Packard HP6890 gas chromatograph interfaced to a MasSpec 2. Separation was achieved on a J & W Scientific DB-5 capillary column, 30 m  $\times$  0.25 mm, 0.25  $\mu\text{m}$  film thickness using helium (30 mL  $\text{s}^{-1}$ ) as carrier gas. Melting point: Büchi B-540 (Büchi Labortechnik AG, CH-9230 Flawil, Switzerland). Chromatography: Silica gel Si 60 (0.200-0.063 mm, E. Merck, Darmstadt, Germany); cellulose microcrystalline Avicel (E. Merck, Darmstadt, Germany).

## Complete Synthetic Scheme



Reagents and conditions: (a) 2 eq. mol LDA, THF, -78°C to reflux; (b) Me<sub>2</sub>SO<sub>4</sub>, DIEA; (c) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>; (d) i) NBS, Me<sub>2</sub>S, CH<sub>2</sub>Cl<sub>2</sub>; ii) (Bu<sub>4</sub>N)<sub>3</sub>P<sub>2</sub>O<sub>7</sub>H, ACN; iii) ion exchange; iv) cellulose, ACN/NH<sub>4</sub>HCO<sub>3</sub>

### Synthetic Procedure:

**(2E) deuterated substrates**

We had recently reported the synthesis and characterization of (2E) deuterated substrates **5a-d**, **7a-d** and **1a-d**. We followed the same protocol for synthesis in these experiments.<sup>1</sup>

**[2,2-<sup>2</sup>H]-Trimethylsilylacetic acid [4].** A mixture of sodium acetate-*d*<sub>3</sub> (1.76 g, 20.7 mmol, Aldrich), 18-crown-6 ether (2g, 7.6 mmol) in dry ether (100 mL) was refluxed 2h under argon. Trimethylsilyl chloride (2.61 mL, 20.7 mmol) was added dropwise and the mixture was refluxed for 24h under argon. After cooling, the mixture was filtrated under argon. The resulting clear solution was added dropwise to a solution of lithium diisopropylamine at -78°C [prepared by reaction of *n*-butyl lithium 1.6 M in hexane (12.94 mL, 20.7 mmol) and diisopropylamine (2.90 mL, 20.7 mmol) in ether (40 mL)]. The mixture was stirred for 30 min at -78°C, warmed to rt and stirring was continued for additional 30 min. The yellow solution was then refluxed for 2h. The reaction was quenched by addition of saturated NH<sub>4</sub>Cl at 0°C. The aqueous phase was acidified to pH = 3 with HCl (0.5 M) and the solution was extracted with ether (3 ø 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. Purification by flash chromatography (1:4 (v/v) ether in petroleum ether) gave **4** (1.16 g, 42 %) as a colorless oil which solidifies at low temperature. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.17 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ (CO<sub>2</sub>H not observed), -1.13; IR (neat) cm<sup>-1</sup>: ν 2925, 2855, 1733, 1461, 1261, 799; ESI-HRMS calcd. for C<sub>4</sub>H<sub>7</sub>D<sub>2</sub>O<sub>2</sub>Si [M-CH<sub>3</sub>]<sup>+</sup> 119.0497, found 119.0501.

**General Procedure for the Preparation of Pentadeuterated Ketones.** A mixture of **3a,c** (39.6 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.25 g, previously dried at 80°C for 24h) in D<sub>2</sub>O (8 mL) was vigorously stirred overnight at 70°C under argon. After cooling to rt, the mixture was extracted with dry CH<sub>2</sub>Cl<sub>2</sub> (3 ø 10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The

procedure was repeated 3-5 times with fresh D<sub>2</sub>O and K<sub>2</sub>CO<sub>3</sub>. The degree of labeling was monitored by GC-MS (>96 atom % <sup>2</sup>H). The pentadeuterated ketone was purified by flash chromatography (1:9 (v/v) ether in petroleum ether).

**[1,1,1,3,3-<sup>2</sup>H<sub>5</sub>]-6-Methyl-hept-5-en-2-one [3b]**. According the general procedure, deuteration of 6-methyl-hept-5-en-2-one **3a** (5g) gave **3b** (4.21 g, 81 %) as a yellow pale oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.0-5.04 (m, 1H), 2.20 (d, *J* = 7.09 Hz, 2H), 1.63 (s, 3H), 1.57 (s, 3H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 209.4, 133.0, 122.9, 25.9, 22.7, 17.9; IR (neat) cm<sup>-1</sup>: ν 2977, 2937, 2554, 1711, 1449, 1380, 1252, 1171, 1042; EI-MS [*M*<sup>+</sup>] 131 (4), 113 (85), 95 (65), 69 (60), 46 (100); ESI-HRMS calcd. for C<sub>8</sub>H<sub>9</sub>D<sub>5</sub>O [*M*]<sup>+</sup>. 131.1358 found 131.1360 [21].

**(5E)-[1,1,1,3,3-<sup>2</sup>H<sub>5</sub>]-6,10-Dimethyl-undeca-5,9-dien-2-one [3d]**. According the general procedure, deuteration of (5E)-6,10-dimethylundeca-5,9-dien-2-one **3c** (5g) gave **3d** (4.41 g, 86 %) as a yellow pale oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.07 (t, *J* = 7.8 Hz, 2H), 2.25 (d, *J* = 6.8 Hz, 2H), 1.95-2.08 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H); IR (neat) cm<sup>-1</sup>: ν 2969, 2920, 2857, 1712, 1449, 1378, 1252, 1175, 1061; EI-MS [*M*<sup>+</sup>] 199 (3), 181 (4), 156 (28), 136 (39), 121 (15), 93 (21), 82 (9), 69 (78), 53 (17), 46 (100); ESI-HRMS calcd. for C<sub>8</sub>H<sub>9</sub>D<sub>5</sub>O [*M*]<sup>+</sup>. 199.1984, found 199.1985 [22].

**General Procedure for the Preparation of Methyl Esters.** Methyl esters were prepared according to the modified method of Arigoni et al. [14]. To a solution of lithium diisopropylamine (2.2 eq. mol) in THF (15 mL) at -78°C was added dropwise a solution of **4** (1.16 g, 8.64 mmol) in THF (15 mL). The mixture was stirred for 30 min at -78°C, 30 min at 0°C and then cooled to -78°C before dropwise addition of the corresponding ketones **3a-d** (1.1 eq. mol) in THF (15 mL). The reaction mixture was then stirred 1h at -78°C, 1h at -10°C and 1h at rt. The reaction mixture was quenched by dropwise addition of HCl (0.1 N) at 0°C. THF was

removed under reduced pressure and the residue was dissolved in hexane (30 mL). The solution was poured into 100 mL of an hexane:HCl (0.5 N) (3:1) mixture and the aqueous phase was extracted with hexane (3  $\times$  40 mL). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Purification by flash chromatography (1:4 (v/v) ether in petroleum ether) gave an isomeric mixture of corresponding carboxylic acids. The mixture of *E/Z* carboxylic acids was dissolved in ACN (20 mL) at 0°C and freshly distilled diisopropylamine (1.1 eq. mol) was added dropwise. The mixture was stirred 10 min at 0°C, 20 min at rt and then cooled to 0°C before dropwise addition of freshly distilled dimethyl sulfate (2 eq. mol). The reaction mixture was stirred for 3h at rt. The mixture was quenched by dropwise addition of NH<sub>4</sub>OH (0.1N) and the solvent was removed under reduced pressure. The residue was taken up in Et<sub>2</sub>O (10 mL), poured into an ether:water (3:1) mixture (80 mL) and the aqueous phase was extracted with ether (3  $\times$  30 mL). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Silica gel column chromatography (1:9 (v/v) ether in petroleum ether) gave isomerically pure methyl esters.

**Methyl (2*E*)-[2-<sup>2</sup>H<sub>1</sub>]-3,7-Dimethylocta-2,6-dienoate [5a] and Methyl (2*Z*)-[2-<sup>2</sup>H<sub>1</sub>]-3,7-Dimethylocta-2,6-dienoate [6a].** According the general procedure, condensation of **1a** (1.14 g) and **2** (1.10 g), esterification of the mixture of *E/Z* carboxylic acids and subsequent purification by flash chromatography gave **6a** (0.20 g) as a colorless oil followed by **5a** (0.31 g) as a colorless oil (total yield 35 % from **2**, *Z/E* 4:6). IR (neat, mixture of *E*- and *Z*- isomers) cm<sup>-1</sup>:  $\nu$  2962, 1261, 1094, 1021, 866, 800.

Data for **6a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.14-5.18 (m, 1H), 3.68 (s, 3H), 2.64 (t, *J* = 8.25 Hz, 2H), 1.69 (q, *J* = 7.52 Hz, 2H), 1.90 (s, 3H); 1.69 (s br, 3H), 1.63 (s br, 3H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  167.1, 160.8, 132.6, 124.5, 51.1, 33.8, 27.2, 26.0, 25.6, 18.0; EI-MS [M]<sup>+</sup> 183

(6), 152 (16), 124 (35), 115 (55), 84 (36), 69 (100), 41 (37); ESI-HRMS calcd. for  $C_{11}H_{17}DO_2$   $[M]^+$  183.1369, found 183.1360.

Data for **5a**:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  5.07-5.10 (m, 1H), 3.69 (s, 3H), 2.17 (s, 7H), 1.69 (s, 3H), 1.61 (s, 3H);  $^{13}C$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  167.6, 160.4, 132.9, 123.4, 51.1, 41.2, 26.4, 26.0, 19.2, 18.1; EI-MS  $[M]^+$  183 (15), 152 (19), 124 (47), 115 (87), 84 (59), 69 (100), 41 (57); ESI-HRMS calcd. for  $C_{11}H_{17}DO_2$   $[M]^+$  183.1369, found 183.1362.

**Methyl (2E)-[2,4,4,9,9,9- $^2H_6$ ]-3,7-Dimethylocta-2,6-dienoate [5b] and Methyl (2Z)-[2,4,4,9,9,9- $^2H_6$ ]-3,7-Dimethylocta-2,6-dienoate [6b]**. According the general procedure, condensation of **3b** (1.25 g) and **2** (1.16 g), esterification of the mixture of *E/Z* carboxylic acids and subsequent purification by flash chromatography gave **6b** (0.24 g) as a colorless oil followed by **5b** (0.37 g) as a colorless oil (total yield 38 % from **2**, *Z/E* 4:6). IR (neat, mixture of *E*- and *Z*-isomers)  $cm^{-1}$ :  $\nu$  2964, 2918, 1719, 1629, 1435, 1230, 1102, 1041, 792.

Data for **6b**:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  5.14-5.18 (m, 1H), 3.68 (s, 3H), 2.15 (d,  $J = 7.30$  Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H);  $^{13}C$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  167.1, 160.5, 132.5, 124.1, 51.1, 27.0, 26.0, 18.0; EI-MS  $[M]^+$  188 (10), 156 (16), 128 (38), 119 (41), 88 (36), 69 (100), 41 (47); ESI-HRMS calcd. for  $C_{11}H_{12}D_6O_2$   $[M]^+$  188.1683, found 188.1691.

Data for **5b**:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  5.07-5.10 (m, 1H), 3.69 (s, 3H), 2.15 (d,  $J = 6.83$  Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H);  $^{13}C$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  167.6, 160.2, 132.9, 123.4, 51.1, 26.3, 26.0, 18.0; EI-MS  $[M]^+$  188 (7), 156 (13), 128 (27), 119 (50), 88 (26), 69 (100), 41 (38); ESI-HRMS calcd. for  $C_{11}H_{12}D_6O_2$   $[M]^+$  183.1683, found 188.1692.

**Methyl (2E,6E)-[2- $^2H_1$ ]-3,7,11-Trimethyldodeca-2,6,10-trienoate [5c] and Methyl (2Z,6E)-[2- $^2H_1$ ]-3,7,11-Trimethyldodeca-2,6,10-trienoate [6c]**. According the general procedure, condensation of **3c** (1.62 g) and **2** (1.02 g), esterification of the mixture of *E/Z* carboxylic acids

and subsequent purification by flash chromatography gave **6c** (0.25 g) as a colorless oil followed by **5c** (0.41 g) as a colorless oil (total yield 35 % from **2**, *Z/E* 4:6). IR (neat, mixture of *E*- and *Z*-isomers)  $\text{cm}^{-1}$ :  $\nu$  2968, 2917, 1719, 1638, 1438, 1378, 1241, 1148, 1069, 928, 792.

Data for **6c**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.14-5.18 (m, 1H), 5.06-5.10 (m, 1H), 3.66 (s, 3H), 2.65 (t,  $J = 7.79$  Hz, 2H), 2.17 (q,  $J = 7.64$  Hz, 2H), 2.03-2.08 (m, 2H), 1.95-1.99 (m, 2H), 1.88 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  167.0, 160.6, 136.1, 131.5, 124.7, 123.9, 50.9, 40.0, 33.7, 27.1, 27.0, 26.0, 25.5, 17.9, 16.2; EI-MS  $[\text{M}]^+$  251 (8), 208 (21), 136 (32), 115 (55), 81 (51), 69 (100), 41 (52); ESI-HRMS calcd. for  $\text{C}_{16}\text{H}_{25}\text{DO}_2$   $[\text{M}]^+$  251.1995, found 251.1999.

Data for **5c**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.07-5.10 (m, 2H), 3.69 (s, 3H), 2.17 (s br, 7H), 1.97-2.10 (m, 4H), 1.69 (s, 3H), 1.61 (s br, 6H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  167.6, 160.3, 136.6, 131.7, 124.6, 123.3, 51.0, 41.3, 40.0, 27.1, 26.4, 26.0, 19.2, 18.0, 16.3; EI-MS  $[\text{M}]^+$  251 (25), 208 (56), 150 (57), 115 (60), 81 (57), 69 (100), 41 (67); ESI-HRMS calcd. for  $\text{C}_{16}\text{H}_{25}\text{DO}_2$   $[\text{M}]^+$  251.1995, found 251.2000.

**Methyl (2*E*,6*E*)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trienoate [5d] and Methyl (2*Z*,6*E*)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trienoate [6d].**

According the general procedure, condensation of **3d** (1.78 g) and **2** (1.09 g), esterification of the mixture of *E/Z* carboxylic acids and subsequent purification by flash chromatography gave **6d** (0.24 g) as a colorless oil followed by **5d** (0.41 g) as a colorless oil (total yield 31 % from **2**, *Z/E* 4:6). IR (neat, mixture of *E*- and *Z*-isomers)  $\text{cm}^{-1}$ :  $\nu$  2967, 2919, 1719, 1629, 1435, 1379, 1226, 1114, 1052.

Data for **6d**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.15-5.19 (m, 1H), 5.07-5.11 (m, 1H), 3.67 (s, 3H), 2.16 (d,  $J = 7.15$  Hz, 2H), 2.03-2.08 (m, 2H), 1.96-1.99 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60

(s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  167.1, 160.7, 136.1, 131.6, 124.7, 123.8, 51.1, 40.0, 27.1, 26.8, 26.0, 18.0, 16.3; EI-MS  $[\text{M}]^+$  256 (3), 213 (5), 119 (30), 81 (24), 69 (100), 41 (34); ESI-HRMS calcd. for  $\text{C}_{16}\text{H}_{20}\text{D}_6\text{O}_2$   $[\text{M}]^+$  256.2309, found 256.2304.

Data for **5d**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (5.07-5.10, m, 2H), 3.69 (s, 3H), 2.16 (d,  $J = 6.61$  Hz, 2H), 1.96-2.09 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  167.6, 160.3, 136.5, 131.8, 124.6, 123.2, 51.1, 40.0, 27.0, 26.2, 26.0, 18.0, 16.4; EI-MS  $[\text{M}]^+$  256 (7), 213 (15), 155 (9), 119 (29), 81 (33), 69 (100), 41 (46); ESI-HRMS calcd. for  $\text{C}_{16}\text{H}_{20}\text{D}_6\text{O}_2$   $[\text{M}]^+$  256.2309, found 256.2302.

**General Procedure for the Preparation of Geraniols and Farnesols.** Geraniols and farnesols were prepared according to the modified method of Arigoni et al. [14]. To a solution of methyl ester **6a-d** (0.87 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at  $-78^\circ\text{C}$  under argon was added dropwise diisobutylaluminium hydride (1M in hexane, 2 eq. mol). Stirring was continued at  $-78^\circ\text{C}$  for 5h before addition of water (0.4 mL), NaOH (1N, 0.4 mL) and water (1.2 mL). The mixture is loaded to a column filled with  $\text{Na}_2\text{SO}_4$  and eluted with MeOH (2 volumes column). The solution is concentrated and purified by flash chromatography (1:4 (v/v) ether in petroleum ether) to give the corresponding alcohol **2a-d**.

**(2Z)-[2- $^2\text{H}_1$ ]-3,7-Dimethylocta-2,6-dien-1-ol [8a].** According the general procedure, reduction of **6a** (0.164 g) gave **8a** (0.126 g, 91 %) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.10-5.14 (m, 1H), 4.10 (s, 2H), 2.10-2.12 (m, 4H), 1.76 (s, 3H), 1.70 (s, 3H), 1.62 (s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  140.3, 132.8, 124.2, 59.4, 32.4, 27.0, 26.0, 23.7, 18.0; ESI-HRMS calcd. for  $\text{C}_{10}\text{H}_{15}\text{D}$   $[\text{M}-\text{H}_2\text{O}]^+$  137.1314, found 137.1306.

**(2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dien-1-ol [8b].** According the general procedure, reduction of **6b** (0.166 g) gave **8b** (0.121 g, 86 %) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

$\delta$  5.11-5.12 (m, 1H), 4.10 (s, 2H), 2.07 (d,  $J = 7.07$  Hz, 2H), 1.70 (s, 3H), 1.62 (s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  140.1, 132.7, 124.2, 59.3, 26.8, 26.0, 18.0.

**(2Z,6E)-[2- $^2\text{H}_1$ ]-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol [8c].** According to the general procedure, reduction of **6c** (0.192 g) gave **8c** (0.160 g, 94 %) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.08-5.12 (m, 2H), 4.09 (s, 2H), 1.95-2.10 (m, 8H), 1.74 (s, 3H), 1.67 (s, 3H), 1.59 (s br, 6H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  140.0, 136.2, 131.7, 124.5, 123.9, 59.2, 40.0, 32.2, 27.0, 26.8, 26.0, 23.7, 18.0, 16.3.

**(2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol [8d].** According to the general procedure, reduction of **6d** (0.155 g) gave **8d** (0.125 g, 91 %) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.07-5.13 (m, 2H), 4.10 (s, 2H), 1.96-2.09 (m, 6H), 1.68 (s, 3H), 1.60 (s, 6H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  140.1, 136.3, 131.8, 124.6, 123.9, 59.3, 40.0, 27.0, 26.7, 26.0, 18.0, 16.3.

**General Procedure for the Preparation of Trisammonium Diphosphates.** Trisammonium diphosphates were prepared according to the modified method of Woodside et al. [15]. To a solution of *N*-chlorosuccinimide (11.39 mmol) in  $\text{CH}_2\text{Cl}_2$  (45 mL) at  $-30^\circ\text{C}$  under argon was added dropwise freshly distilled dimethyl sulfide (1.1 eq. mol). The mixture was warmed to  $0^\circ\text{C}$ , stirred at this temperature for 10 min and cooled to  $-40^\circ\text{C}$ . A solution of alcohol **8a-d** (1 eq. mol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was slowly added before the reaction mixture was warmed to  $0^\circ\text{C}$ . Stirring was continued for 2h at  $0^\circ\text{C}$  and 15 min at rt. The clear solution was then washed with cold saturated NaCl (25 mL). The aqueous phase was extracted with pentane (2  $\times$  20 mL). The combined organic layers were washed with cold saturated NaCl (20 mL), dried ( $\text{MgSO}_4$ ), concentrated under reduced pressure (no water bath) and completely removed under high vacuum for 2h. Corresponding alkyl chlorides were used without further purification. Freshly prepared

tris(tetrabutylammonium) hydrogen pyrophosphate (according the method of Woodside et al. [16]) (1.2 eq. mol) was dissolved in ACN (5 mL) at rt under argon before dropwise addition of alkyl chloride in ACN (2 mL). Stirring was continued at rt overnight. The mixture was concentrated under reduced pressure. The residue was dissolved in  $(\text{NH}_4)_2\text{CO}_3$  (3 mL) (0.25 mM, 2 % isopropyl alcohol), loaded onto a 2  $\times$  30 cm column of Dowex 50WX8-200 ( $\text{NH}_4^+$  form) before elution of two volumes column of  $(\text{NH}_4)_2\text{CO}_3$  (0.25 mM, 2 % isopropyl alcohol). The eluent was lyophilized and the resulting white powder was purified by chromatography on cellulose (1:9 (v/v) water in ACN). Fractions were monitored by TLC (silica gel, *iPr*-OH-water-AcOEt 6:3:1) and those containing trisammonium diphosphate were combined. Solvents were removed under reduced pressure and the resulting solution was lyophilized to afford **2a-d**.

**Trisammonium (2Z)-[2- $^2\text{H}_1$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate [2a].** According the general procedure, phosphorylation of **8a** (0.126 g) gave **2a** (0.187 g, 63 % from **8a**) as a flocculent white solid. mp: 158-159°C.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  5.36-5.38 (m, 1H), 4.63 (d,  $J = 6.24$  Hz, 2H), 2.30-2.37 (m, 4H), 1.94 (s, 3H), 1.87 (s, 3H), 1.81 (s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  145.1, 136.6, 126.8, 64.9 (d,  $J = 5.14$  Hz), 34.1, 28.9, 27.7, 25.4, 19.8;  $^{31}\text{P}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  - 5.60 (d,  $J = 21.73$  Hz, 1 P), - 9.61 (d,  $J_{31\text{P},31\text{P}} = 23.71$  Hz, 1 P); IR (ZnS, microscope)  $\text{cm}^{-1}$ :  $\nu$  3172-2860 (br), 2350, 1860, 1687, 1441, 1203, 1080, 911; ESI-HRMS calcd. for  $\text{C}_{10}\text{H}_{18}\text{DO}_7\text{P}_2$  [ $\text{M}-\text{H}$ ] $^-$  314.0669, found 314.0689.

**Trisammonium (2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate [2b].** According the general procedure, phosphorylation of **8b** (0.121 g) gave **2b** (0.196 g, 70 % from **8b**) as a flocculent white solid. mp: 157-161°C.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  5.36-5.39 (m, 1H), 4.60 (under  $\text{D}_2\text{O}$  pick, s br, 2H), 2.29 (d,  $J = 6.97$  Hz, 2H), 1.87 (s, 3H), 1.80 (s, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  143.8.1, 136.5, 127.1, 65.0 (d,  $J = 5.14$  Hz), 29.0, 28.0,

20.1;  $^{31}\text{P}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  - 5.63 (d,  $J = 53.64$  Hz, 1 P), - 9.61 (d,  $J_{31\text{P},31\text{P}} = 53.64$  Hz, 1 P); IR (ZnS, microscope)  $\text{cm}^{-1}$ :  $\nu$  3185-2854 (br), 2196, 1892, 1649, 1445, 1204, 1087, 916; ESI-HRMS calcd. for  $\text{C}_{10}\text{H}_{13}\text{D}_6\text{O}_7\text{P}_2$   $[\text{M}-\text{H}]^-$  319.0983, found 319.0979.

**Trisammonium (2Z,6E)-[2- $^2\text{H}_1$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl Diphosphate [2c].**

According the general procedure, phosphorylation of **8c** (0.160 g) gave **2c** (0.255 g, 82 % from **2c**) as a flocculent white solid. mp: 184-186°C.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  5.45-5.51 (m, 2H), 4.74 (d,  $J = 6.24$  Hz, 2H), 2.37-2.46 (m, 6H), 2.29-2.33 (m, 2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.91 (s, 6H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  145.2, 139.5, 136.1, 127.3, 127.0, 64.9 (d,  $J = 5.14$  Hz), 41.7, 34.1, 29.0, 28.7, 27.7, 25.5, 19.8, 18.1;  $^{31}\text{P}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  -5.62 (d,  $J = 15.8$  Hz, 1 P), -9.61 (d,  $J_{31\text{P},31\text{P}} = 17.76$  Hz, 1 P); IR (ZnS, microscope)  $\text{cm}^{-1}$ :  $\nu$  3199-2826 (br), 2330, 1914, 1658, 1448, 1205, 1088, 1021, 921; ESI-HRMS calcd. for  $\text{C}_{15}\text{H}_{26}\text{DO}_7\text{P}_2$   $[\text{M}-\text{H}]^-$  382.1295, found 382.1252.

**Trisammonium(2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl**

**Diphosphate [2d].** According the general procedure, phosphorylation of **8d** (0.125 g) gave **2d** (0.135 g, 56 % from **8d**) as a flocculent white solid. mp: 186-188°C.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  5.32-5.38 (m, 2H), 4.61 (d,  $J = 5.97$  Hz, 2H), 2.26-2.28 (m, 4H), 2.18-2.20 (m, 2H), 1.84 (s, 3H), 1.78 (s, 6H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  145.2, 139.7, 136.3, 127.4, 127.1, 65.0 (d,  $J = 4.59$  Hz), 41.9, 27.0, 28.8, 27.9, 20.0, 18.3;  $^{31}\text{P}$  NMR (400 MHz,  $\text{D}_2\text{O}/\text{ND}_4\text{OD}$ )  $\delta$  -6.71 (d,  $J = 15.80$  Hz, 1 P), -9.78 (d,  $J_{31\text{P},31\text{P}} = 11.85$  Hz, 1 P); IR (ZnS, microscope)  $\text{cm}^{-1}$ :  $\nu$  3192-2861 (br), 2332, 2200, 1651, 1446, 1206, 1092, 917; ESI-HRMS calcd. for  $\text{C}_{15}\text{H}_{21}\text{D}_6\text{O}_7\text{P}_2$   $[\text{M}-\text{H}]^-$  387.1609, found 387.1656.

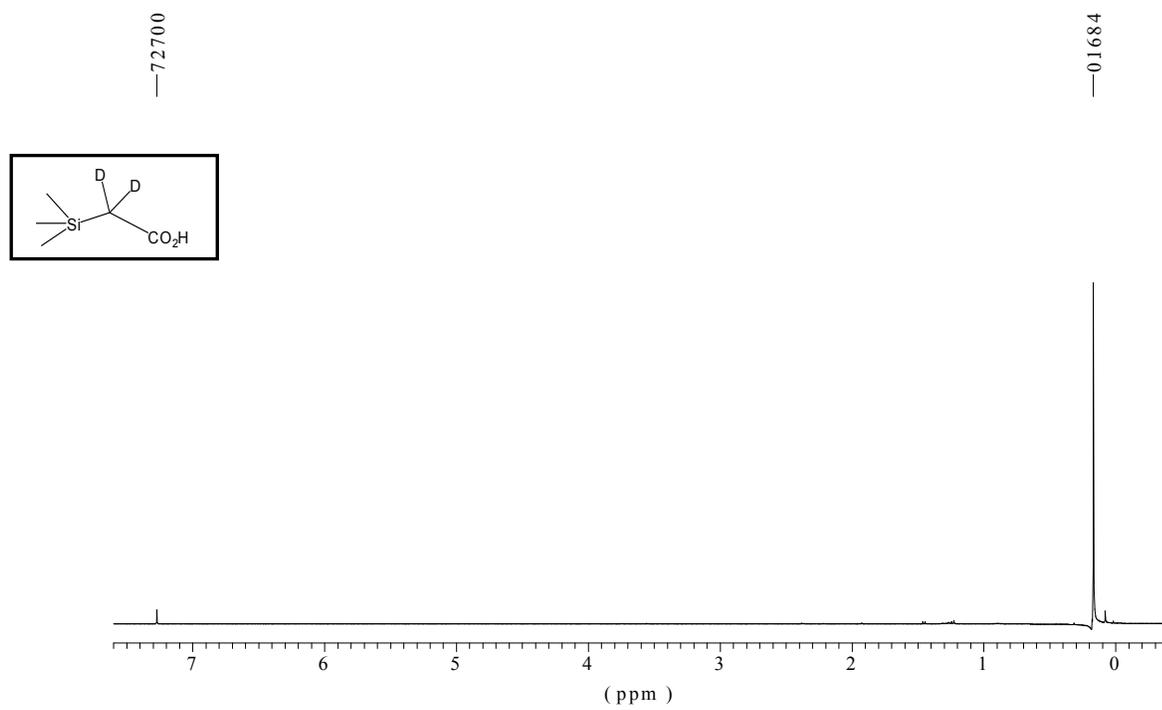
**Heterologous expression of terpene synthases.** The open reading frames of *tps4-B73* and *tps5-Dell* were cloned as *EcoRI-NotI* fragments and inserted into the bacterial expression vector

pHis8-3 which provided the expressed proteins with a His-tag at the *N*-terminal [23]. The constructs were transformed into the *Escherichia coli* strain BL21 (DE3) and fully sequenced to avoid errors introduced by DNA amplification. The recombinant proteins TPS4 and TPS5 were purified from *E. coli* as previously described [9].

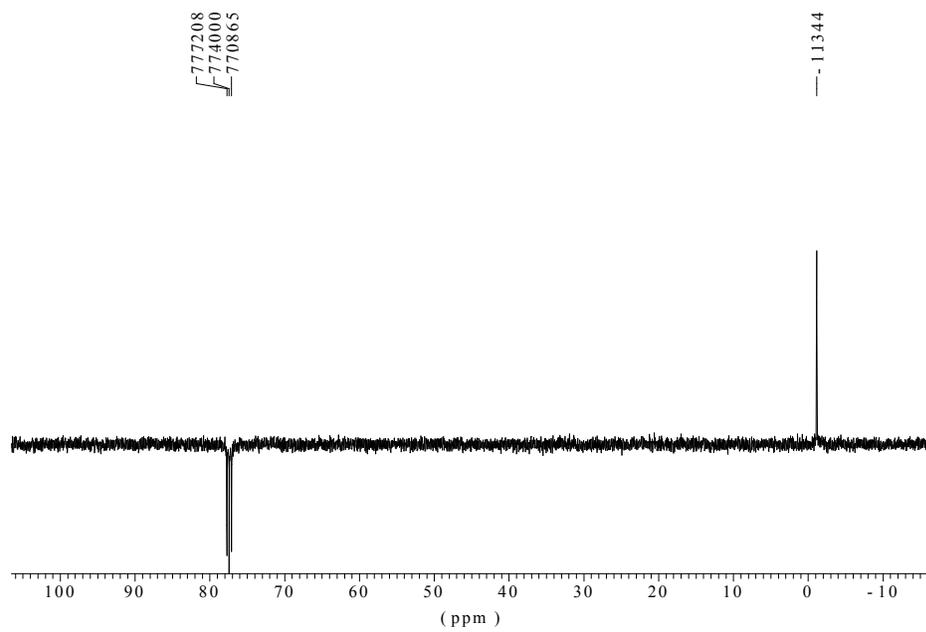
**Assay for terpene synthase activity.** Each 200  $\mu\text{L}$  assay contained 50  $\mu\text{L}$  of the bacterial extract in assay buffer (10 mM 3-(*N*)-2-hydroxypropane sulfonic acid (Mopso), pH 7.0, 1 mM DTT, and 10 % (v/v) glycerol) with 350  $\mu\text{M}$  substrate, 7.5 mM  $\text{MgCl}_2$ , 1.5 mM  $\text{NaWO}_4$ , and 0.75 mM NaF in a 2 ml screw-capped glass vial. The assay was overlaid with 100  $\mu\text{L}$  pentane containing 2.5  $\mu\text{M}$  (*E*)- $\beta$ -caryophyllene (Aldrich, 98 % pure) as an internal standard and incubated for 20 min at 30°C. The reaction was stopped by mixing for 1 min, and an aliquot of the pentane layer was analyzed by GC-FID. Assay results are reported as the mean of three to six independent replicate assays. Product identification was performed by GC-MS as previously described.<sup>2</sup>

**Gas chromatography for terpene synthase activity.** A Hewlett-Packard model 6890 gas chromatograph was employed with the carrier gas He at 1 ml min<sup>-1</sup>, splitless injection (injector temperature: 220°C, injection volume: 2  $\mu\text{L}$ ), a DB-WAX column (polyethylene glycol, 30 m  $\varnothing$  0.25 mm ID  $\varnothing$  0.25  $\mu\text{m}$  film thickness, J&W Scientific, Folsom, CA, USA) for sesquiterpenes and a DB5-MS column (30 m  $\varnothing$  0.25 mm ID  $\varnothing$  0.25  $\mu\text{m}$  film thickness, J & W Scientific) for monoterpenes, respectively. Temperature was programmed from 50°C (3 min hold) at 7°C min<sup>-1</sup> to 240°C (2 min hold). Quantification was performed with the trace of a flame ionization detector (FID) operated at 250°C. Peaks were compared with that of the internal standard assuming equal response factors.

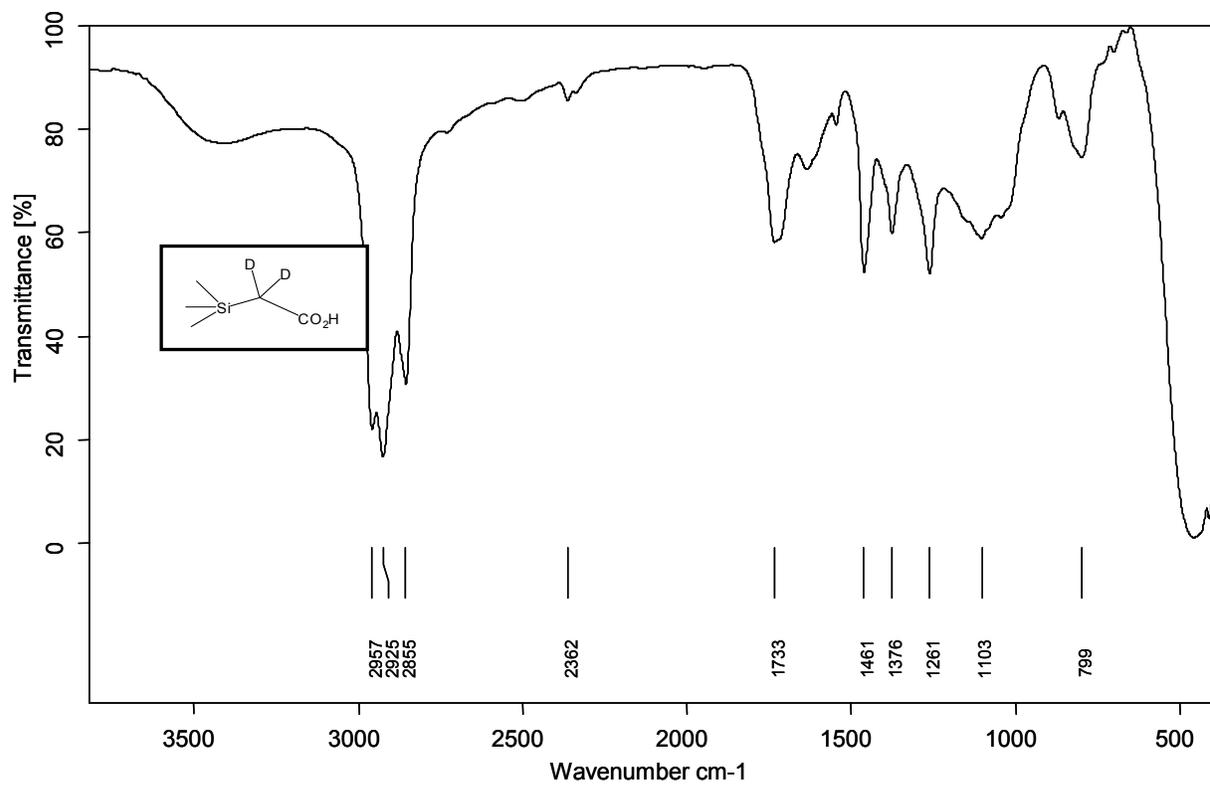
**<sup>1</sup>H NMR of [2,2-<sup>2</sup>H<sub>2</sub>]-Trimethylsilylacetic acid (4)**



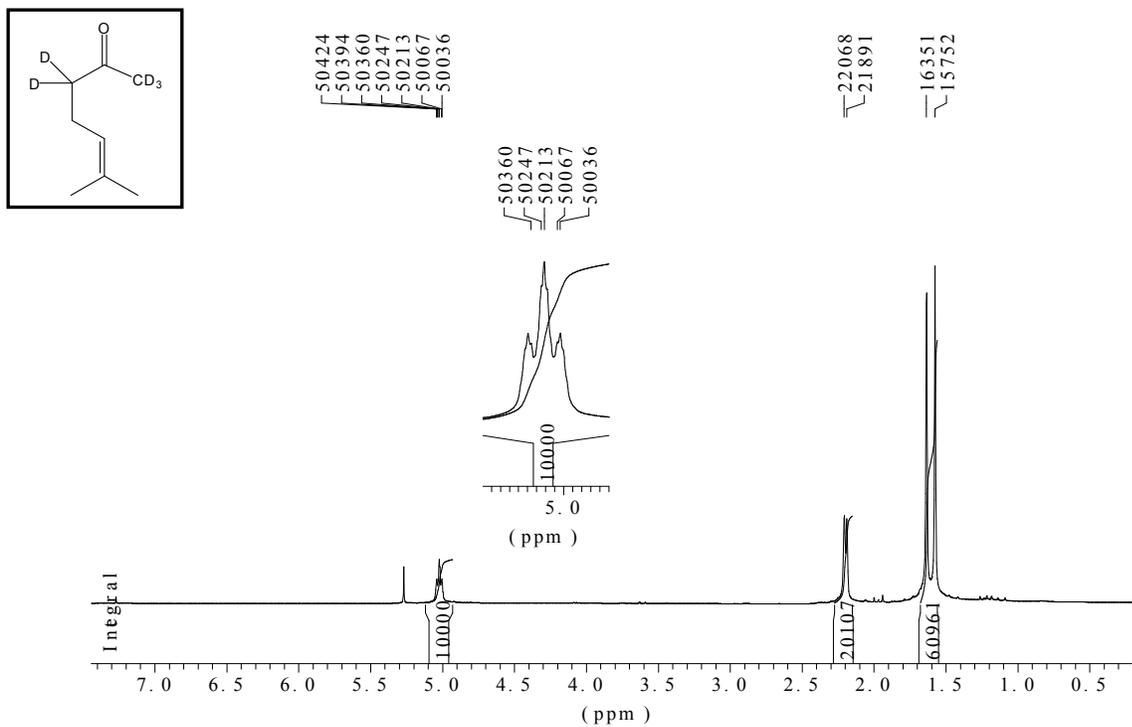
### <sup>13</sup>C NMR of [2,2-<sup>2</sup>H<sub>2</sub>]-Trimethylsilacetic acid (4)



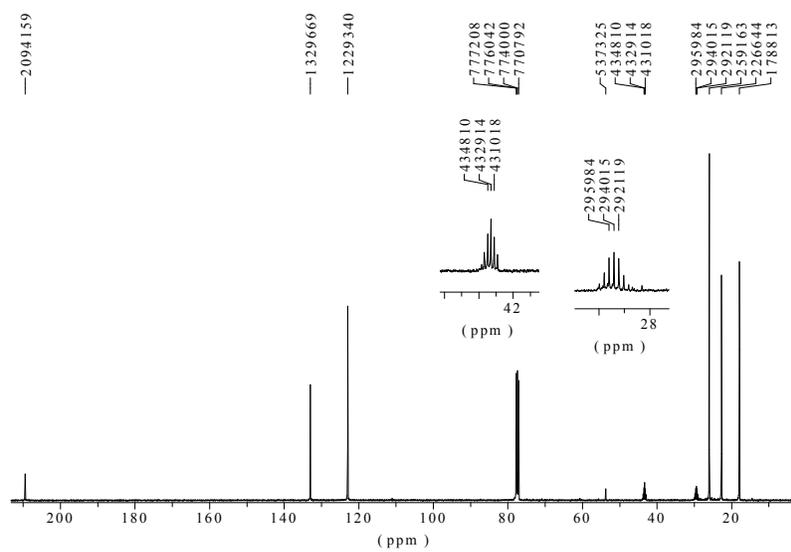
### IR of [2,2-<sup>2</sup>H<sub>2</sub>]-Trimethylsilacetic acid (4)



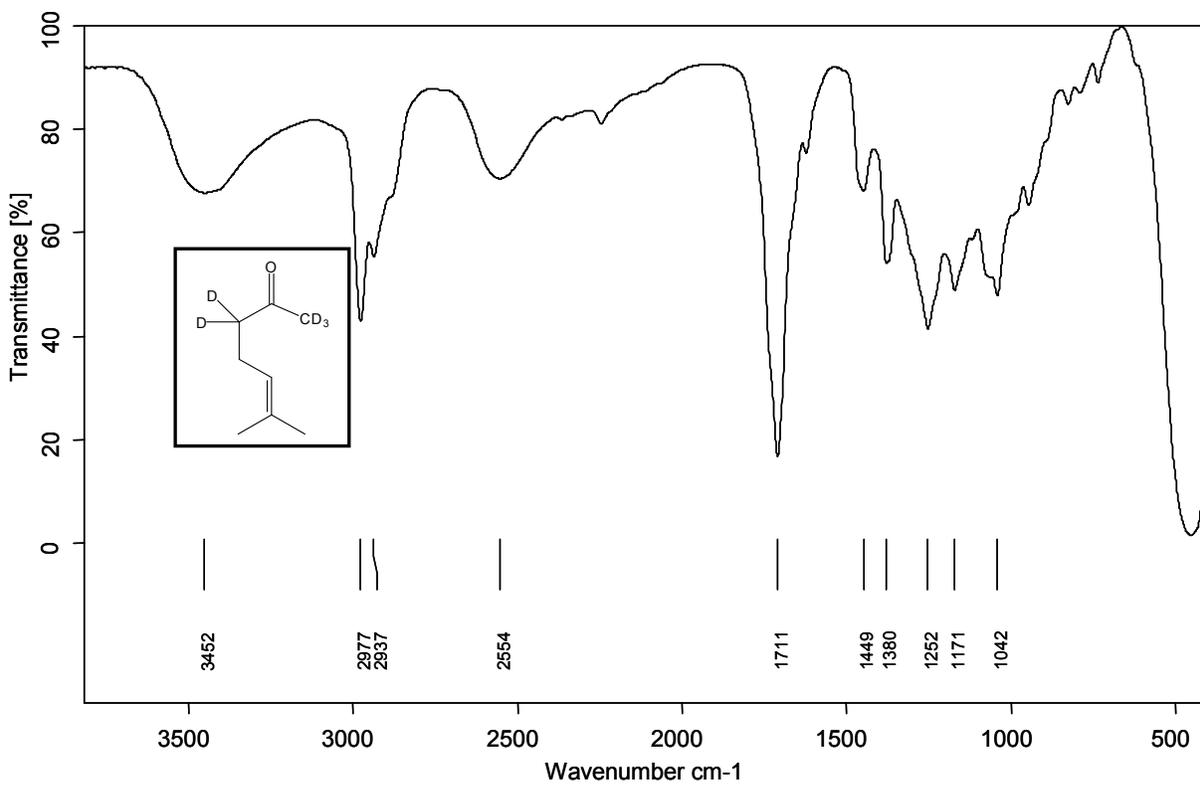
**<sup>1</sup>H NMR of [1,1,1,3,3-<sup>2</sup>H<sub>5</sub>]-6-Methyl-hept-5-en-2-one (3b)**



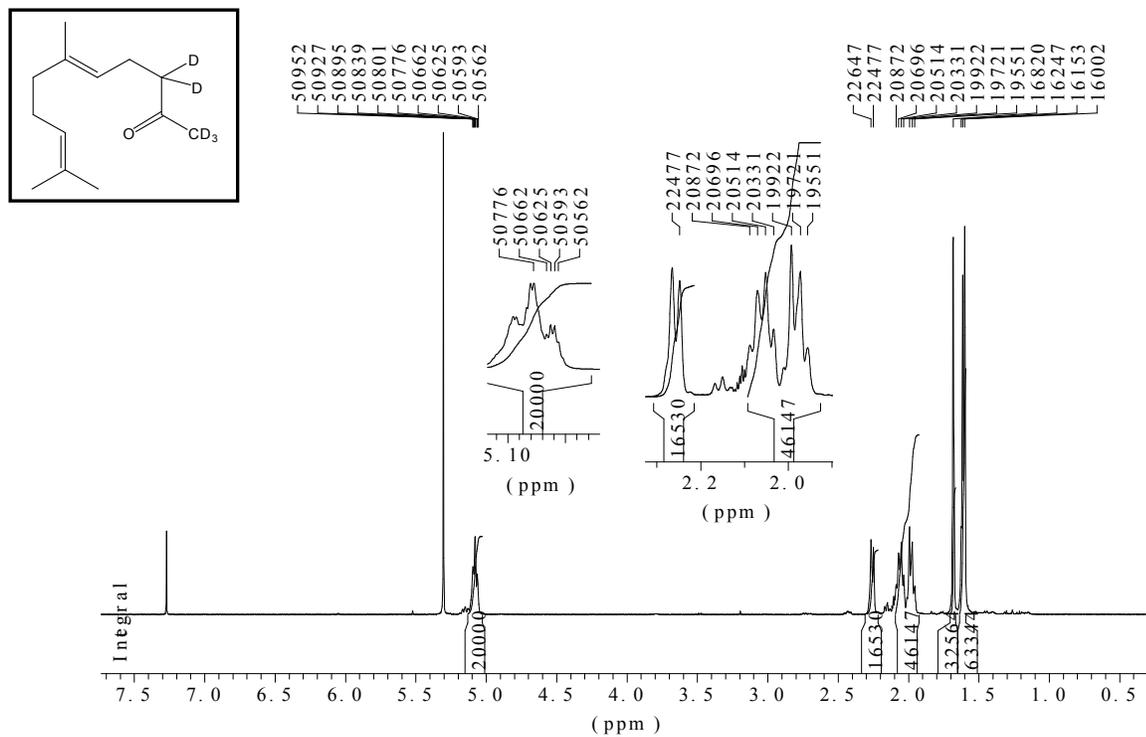
**<sup>13</sup>C NMR of [1,1,1,3,3-<sup>2</sup>H<sub>5</sub>]-6-Methyl-hept-5-en-2-one (3b)**



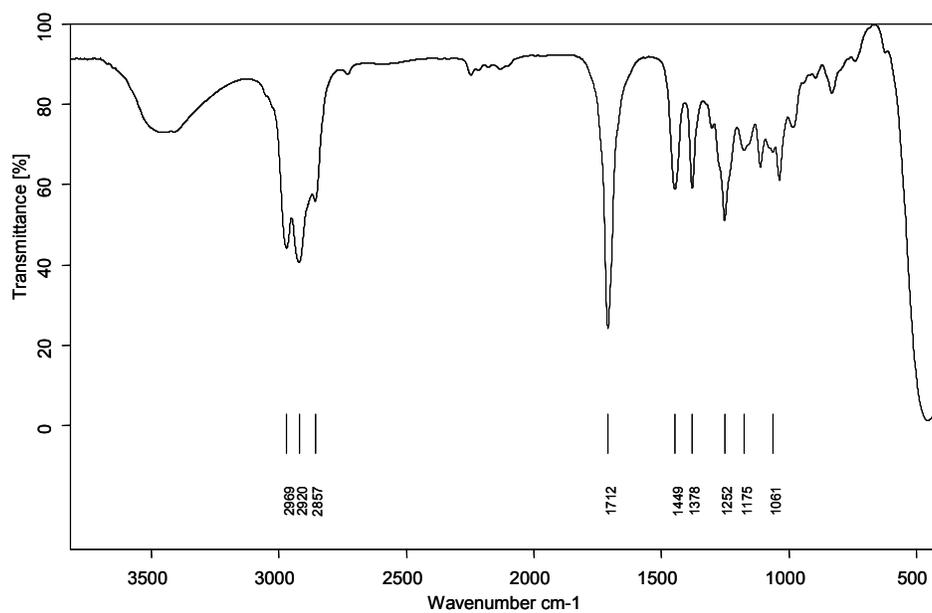
**IR of [1,1,1,3,3-<sup>2</sup>H<sub>5</sub>]-6-Methyl-hept-5-en-2-one (3b)**



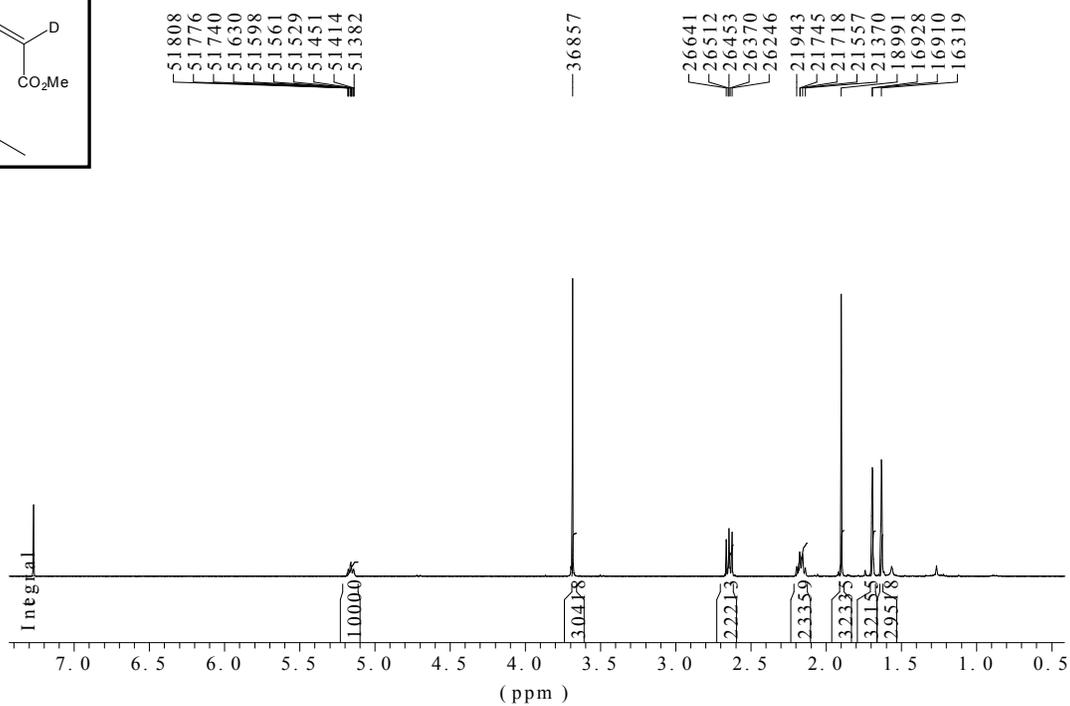
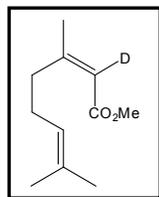
<sup>1</sup>H NMR of [1,1,1,3,3-<sup>2</sup>H<sub>5</sub>]-6,10-Dimethyl-undeca-5,9-dien-2-one (3d)



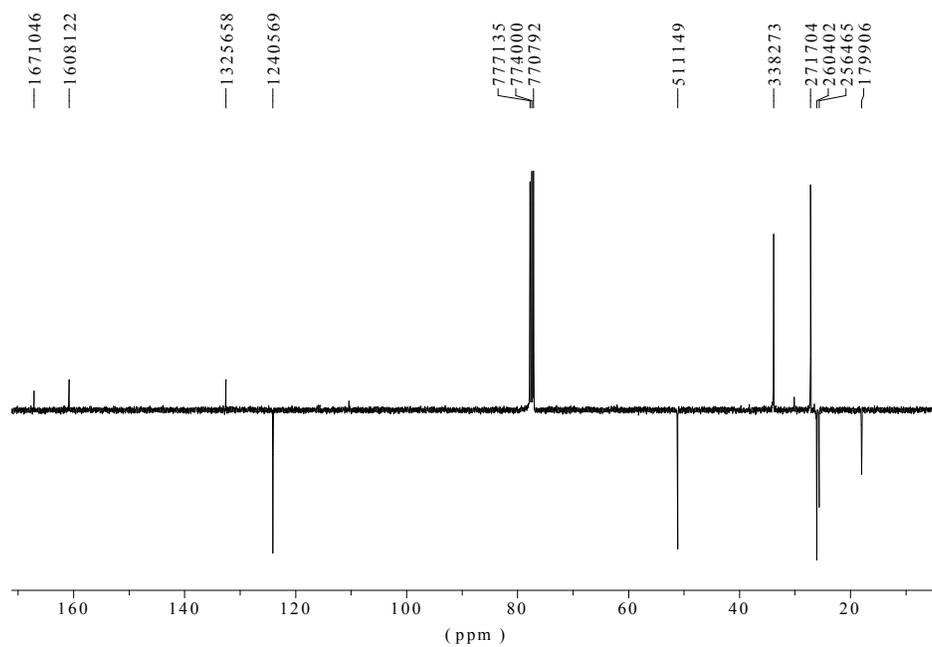
**IR of [1,1,1,3,3-<sup>2</sup>H<sub>5</sub>]-6,10-Dimethyl-undeca-5,9-dien-2-one (3d)**

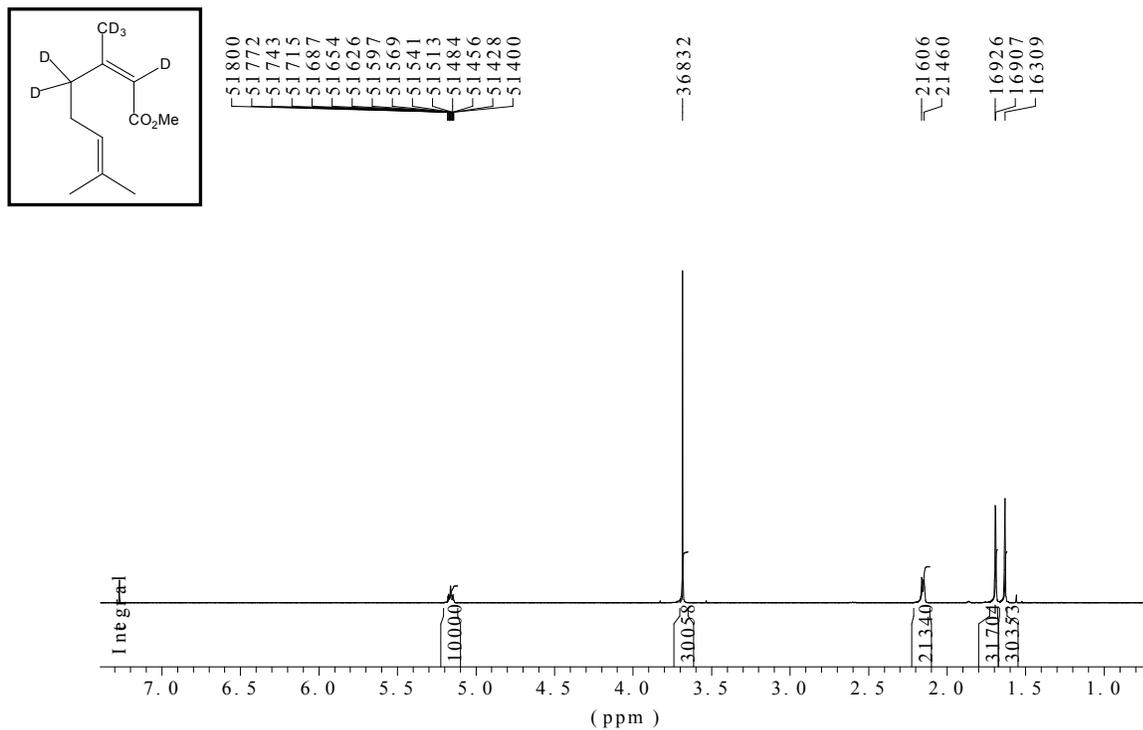
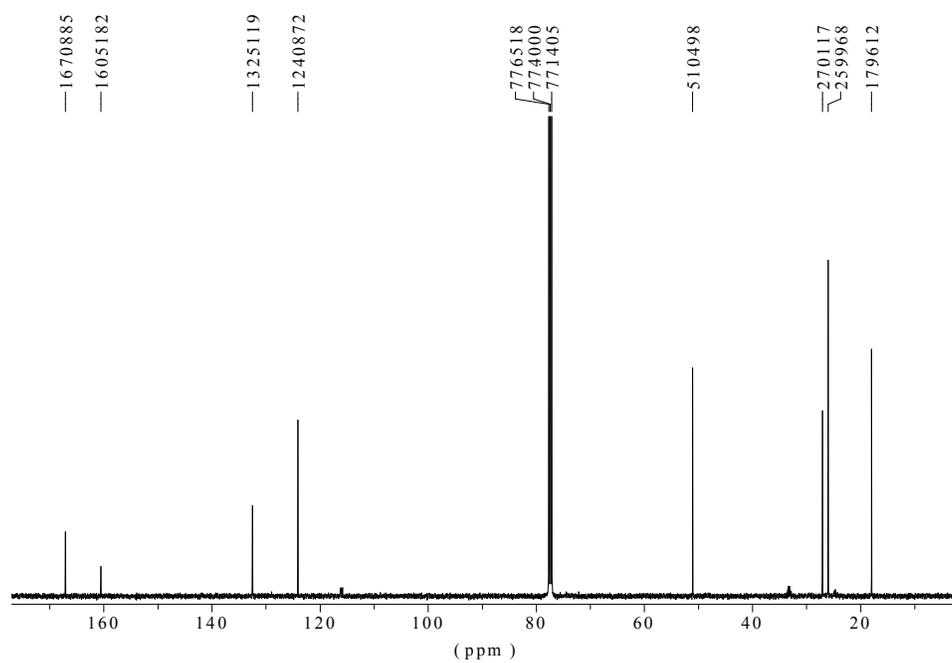


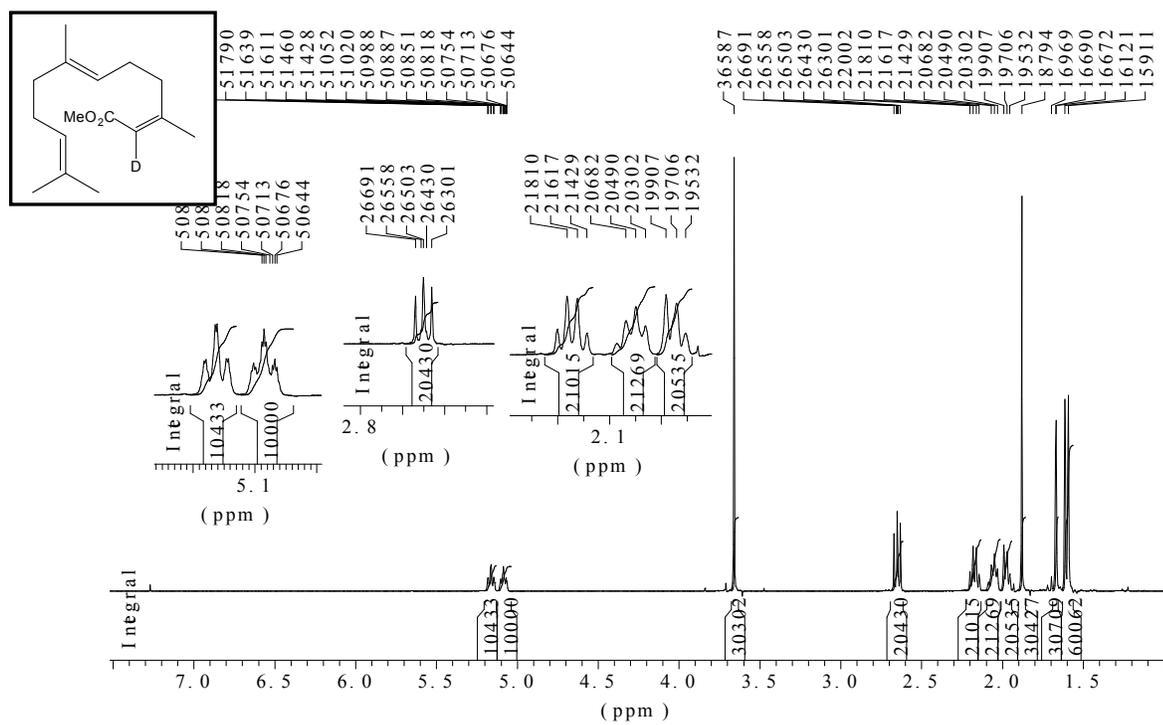
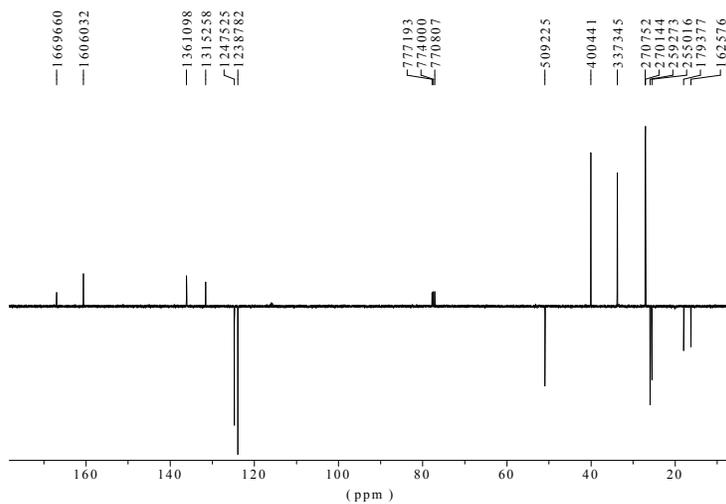
**<sup>1</sup>H NMR of Methyl (2Z)-[2-<sup>2</sup>H]-3,7-Dimethylocta-2,6-dienoate (6a)**



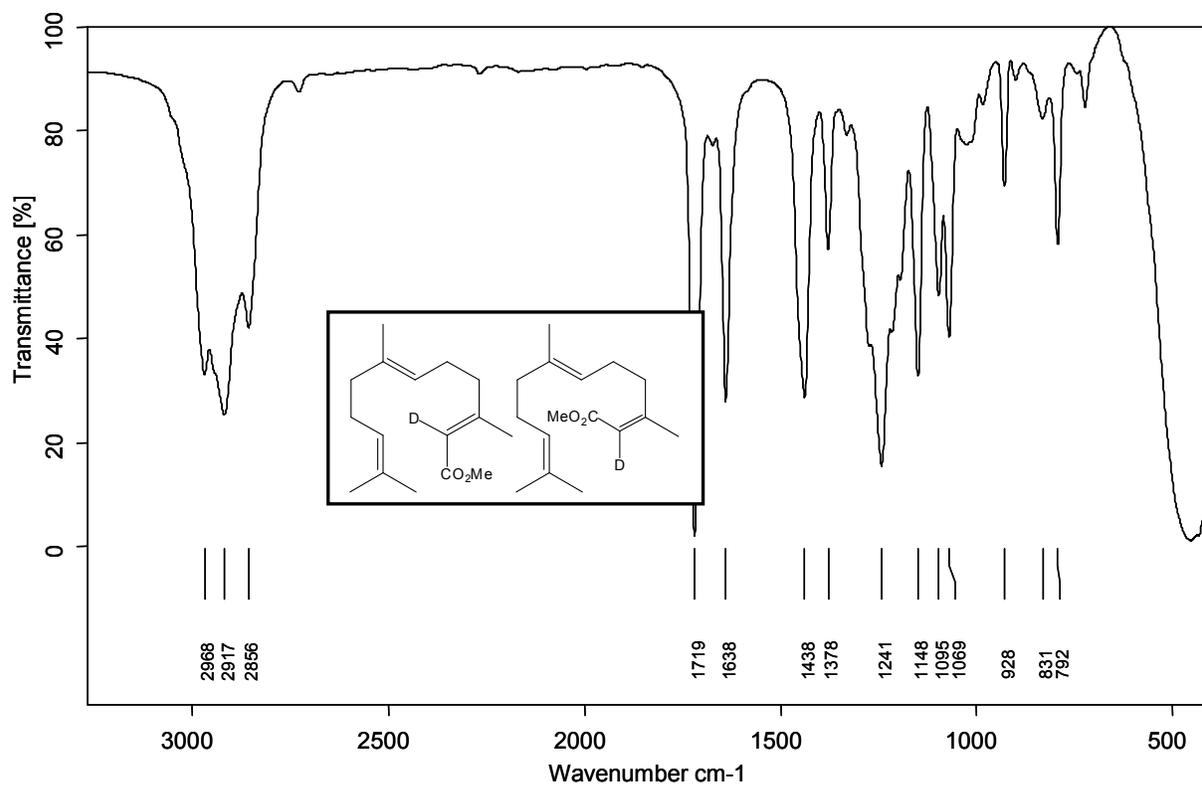
**<sup>13</sup>C NMR of Methyl (2Z)-[2-<sup>2</sup>H]-3,7-Dimethylocta-2,6-dienoate (6a)**

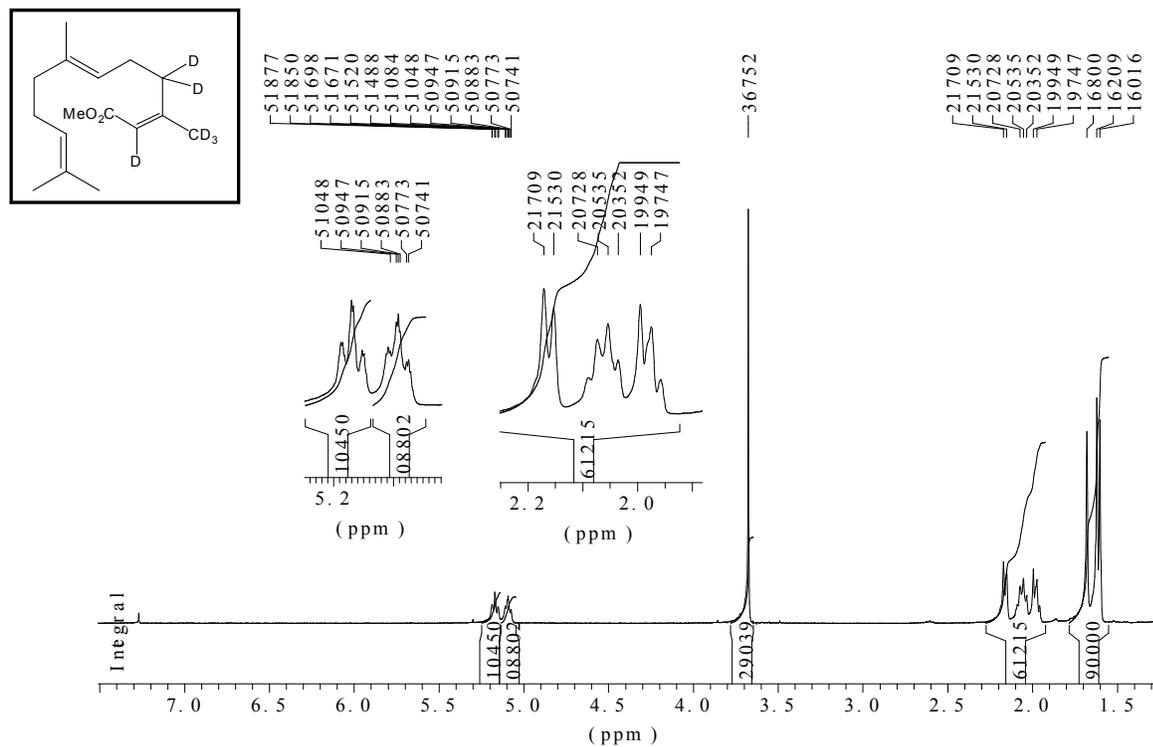
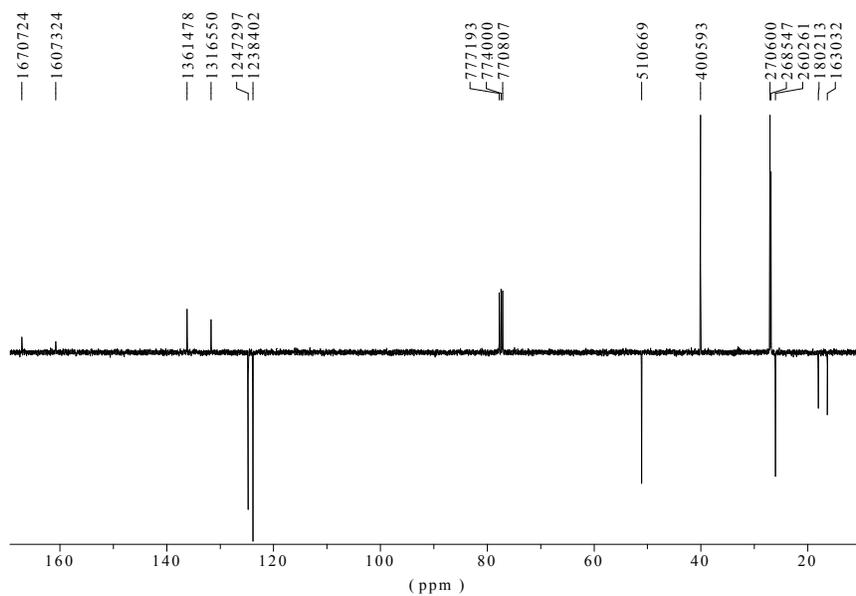


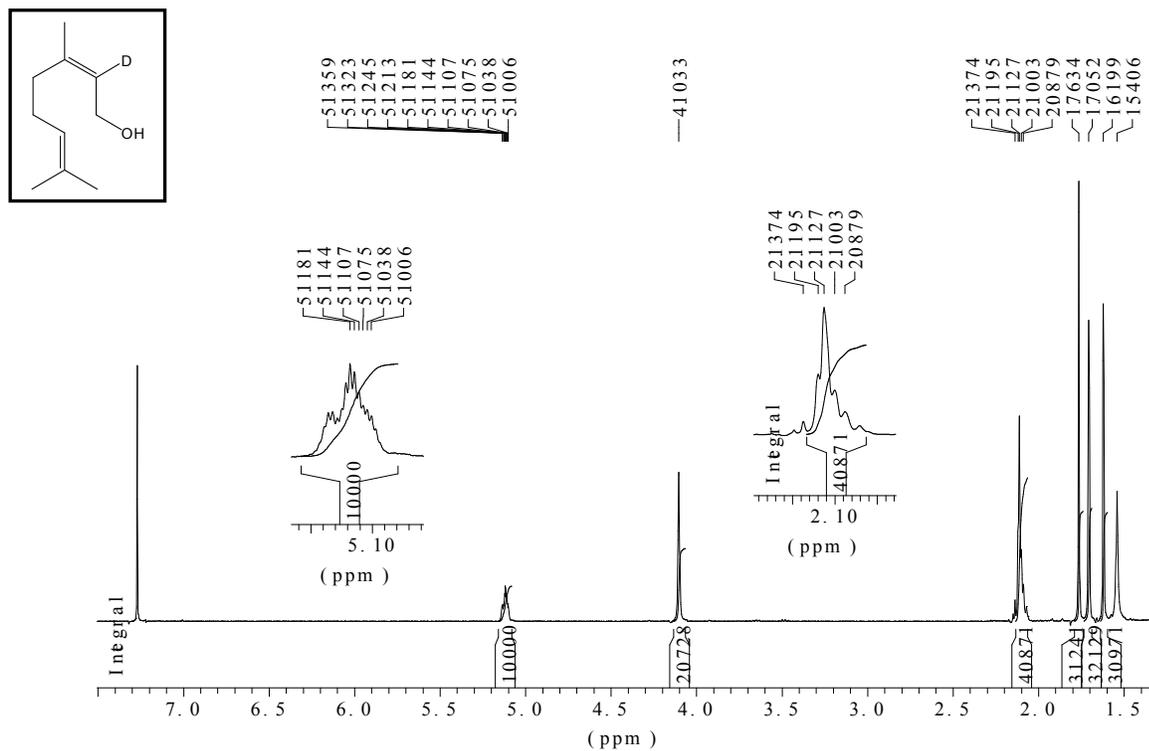
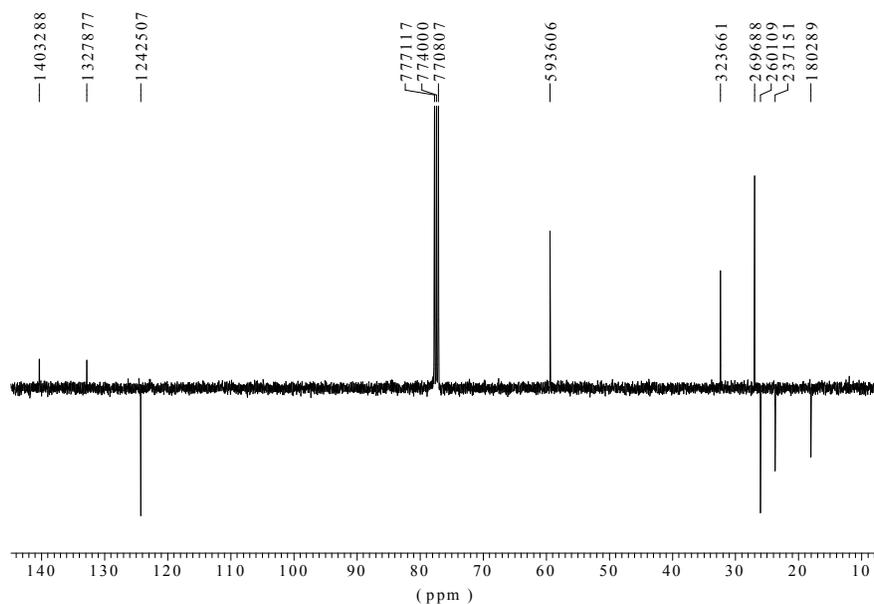
**$^1\text{H}$  NMR of Methyl (2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dienoate (6b)** **$^{13}\text{C}$  NMR of Methyl (2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dienoate (6b)**

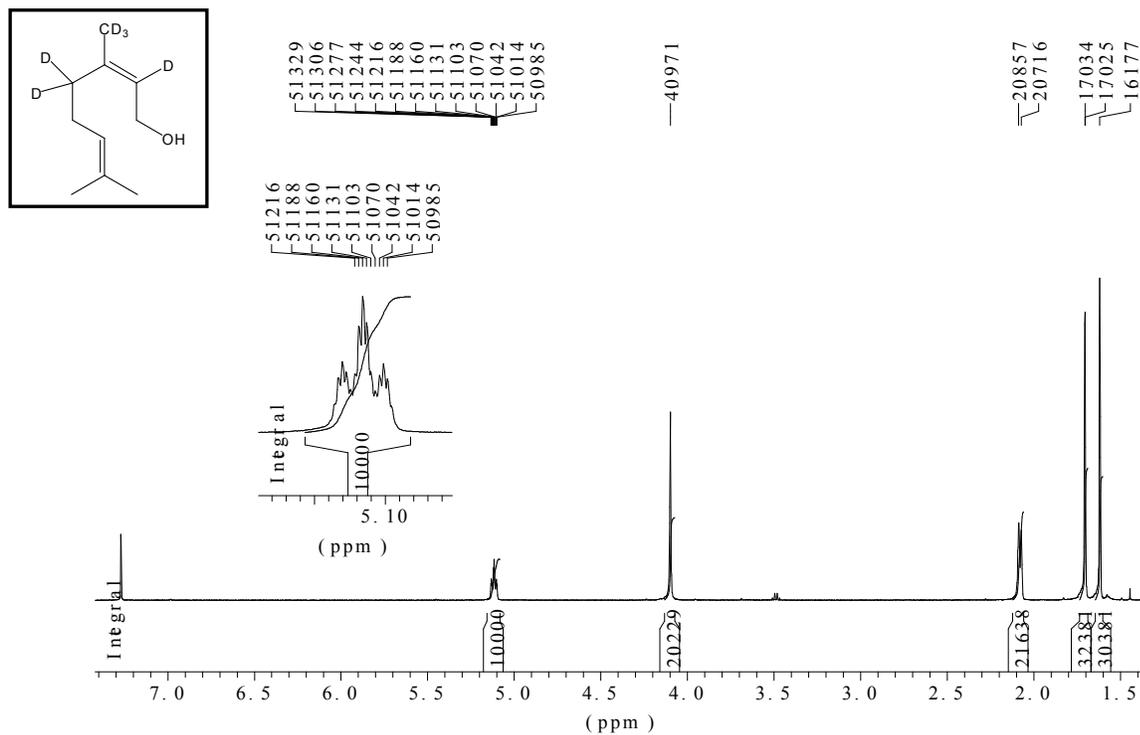
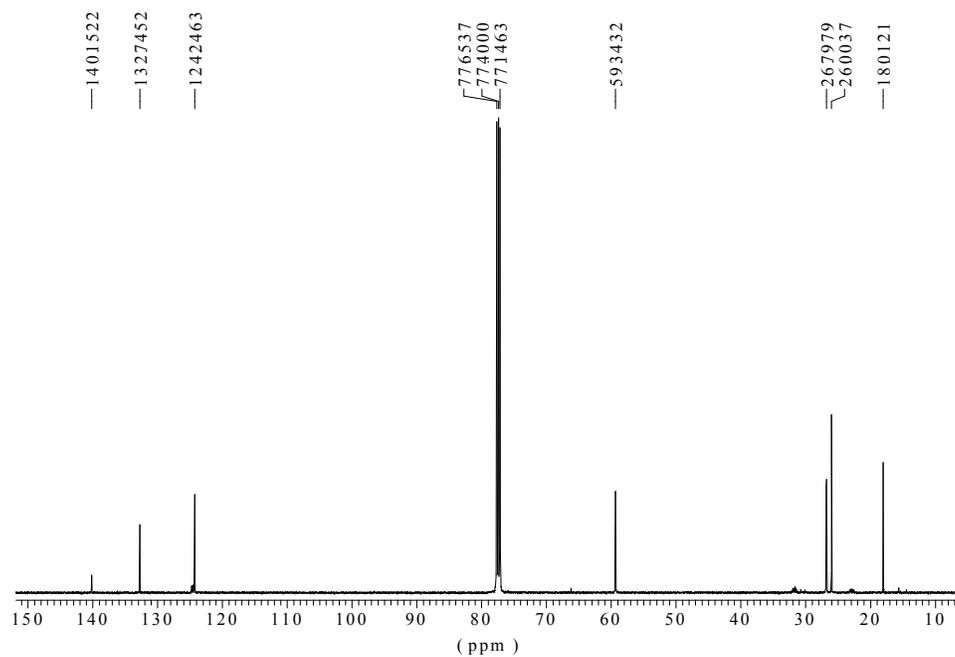
**<sup>1</sup>H NMR of Methyl (2*Z*,6*E*)-[2-<sup>2</sup>H]-3,7,11-Trimethyldodeca-2,6,10-trienoate (6c)****<sup>13</sup>C NMR of Methyl (2*Z*,6*E*)-[2-<sup>2</sup>H]-3,7,11-Trimethyldodeca-2,6,10-trienoate (6c)**

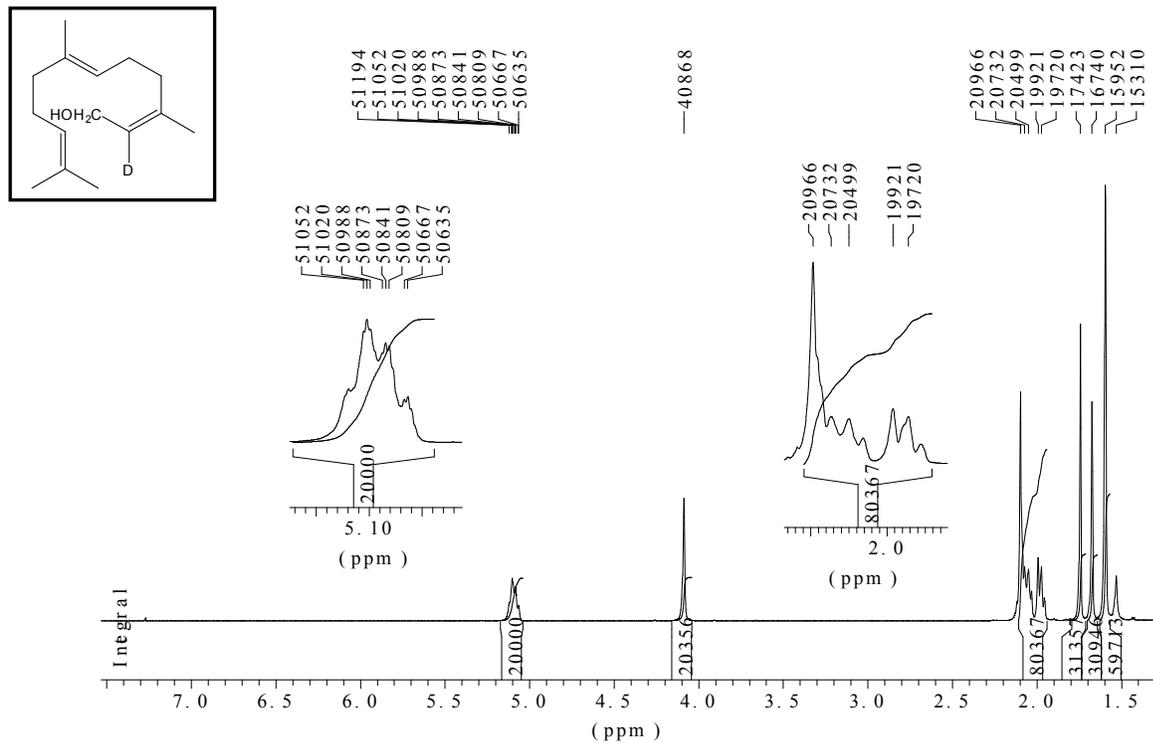
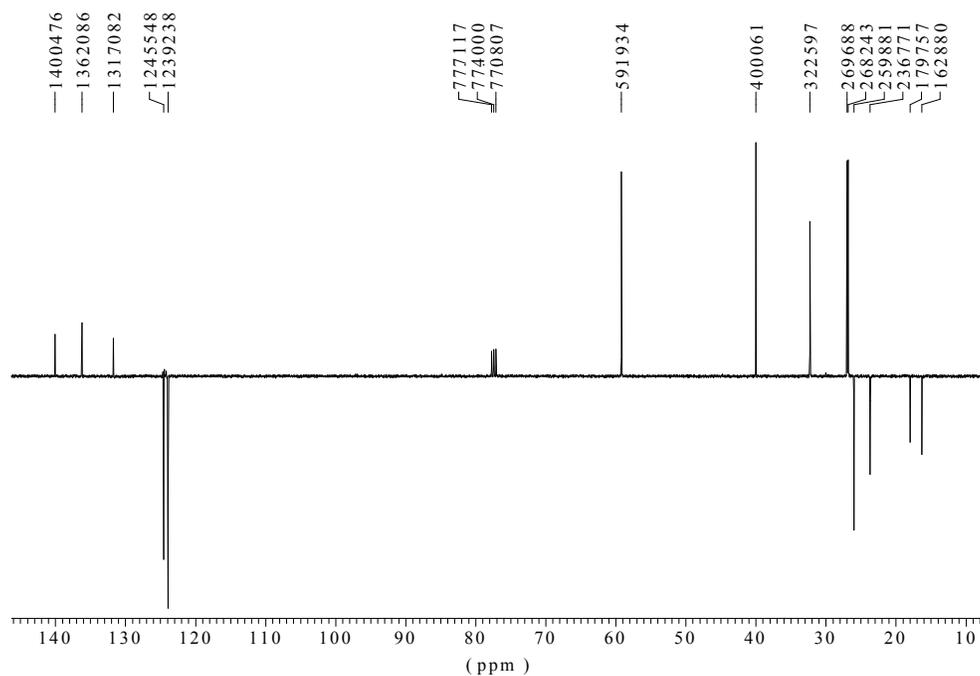
**IR of Methyl (2*E*,6*E*)-[2-<sup>2</sup>H]-3,7,11-Trimethyldodeca-2,6,10-trienoate (3c) and Methyl (2*Z*,6*E*)-[2-<sup>2</sup>H]-3,7,11-Trimethyldodeca-2,6,10-trienoate (6c)**

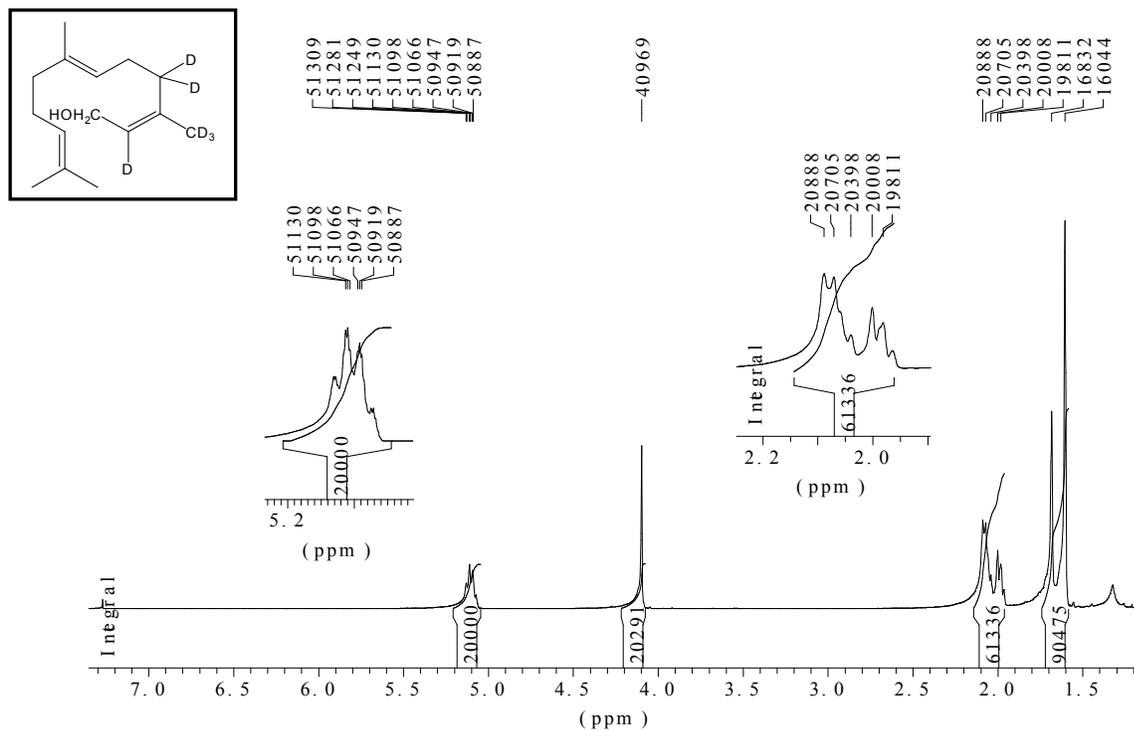
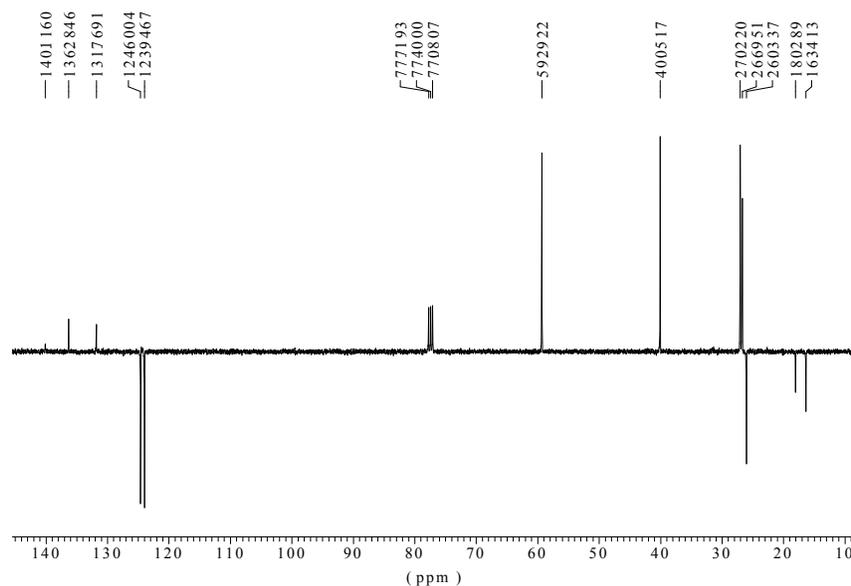


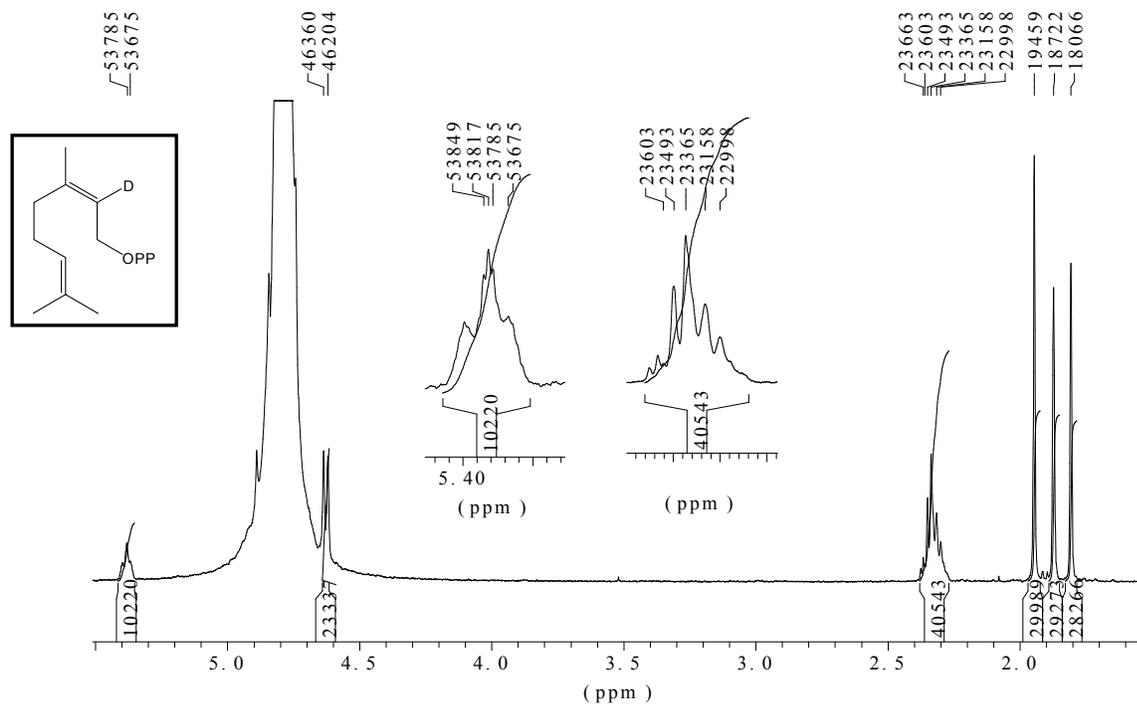
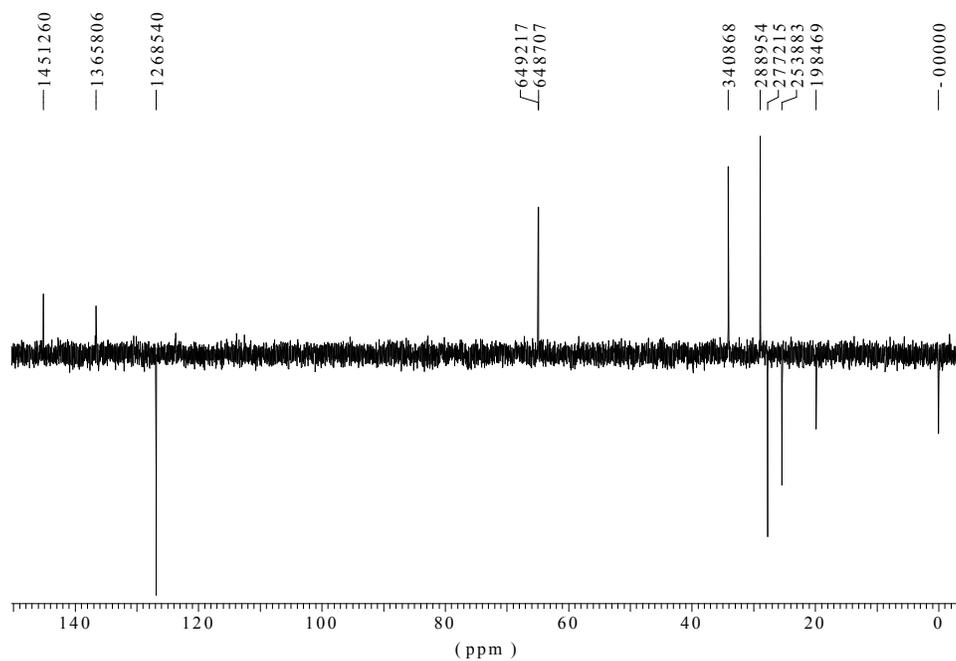
**$^1\text{H}$  NMR of Methyl (2*Z*,6*E*)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-Trimethyldodeca-2,6,10-trienoate (6d)** **$^{13}\text{C}$  NMR of Methyl (2*Z*,6*E*)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-Trimethyldodeca-2,6,10-trienoate (6d)**

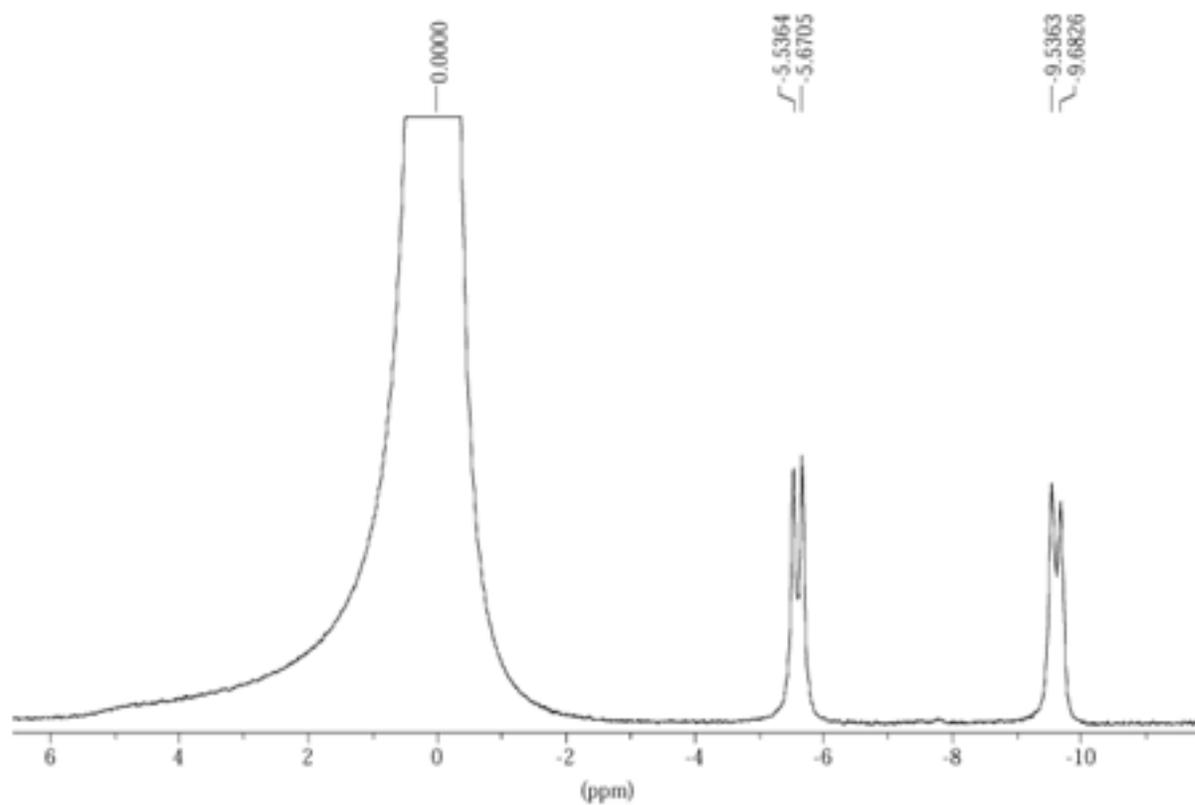
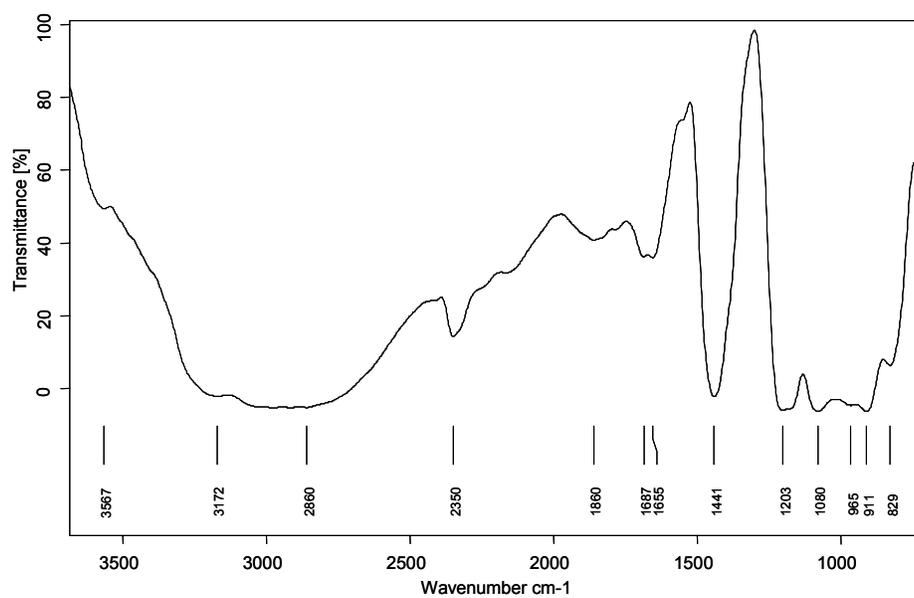
**<sup>1</sup>H NMR of (2Z)-[2-<sup>2</sup>H]-3,7-Dimethylocta-2,6-dien-1-ol (8a)****<sup>13</sup>C NMR of (2E)-[2-<sup>2</sup>H]-Geraniol - (2E)-[2-<sup>2</sup>H]-3,7-Dimethylocta-2,6-dien-1-ol (8a)**

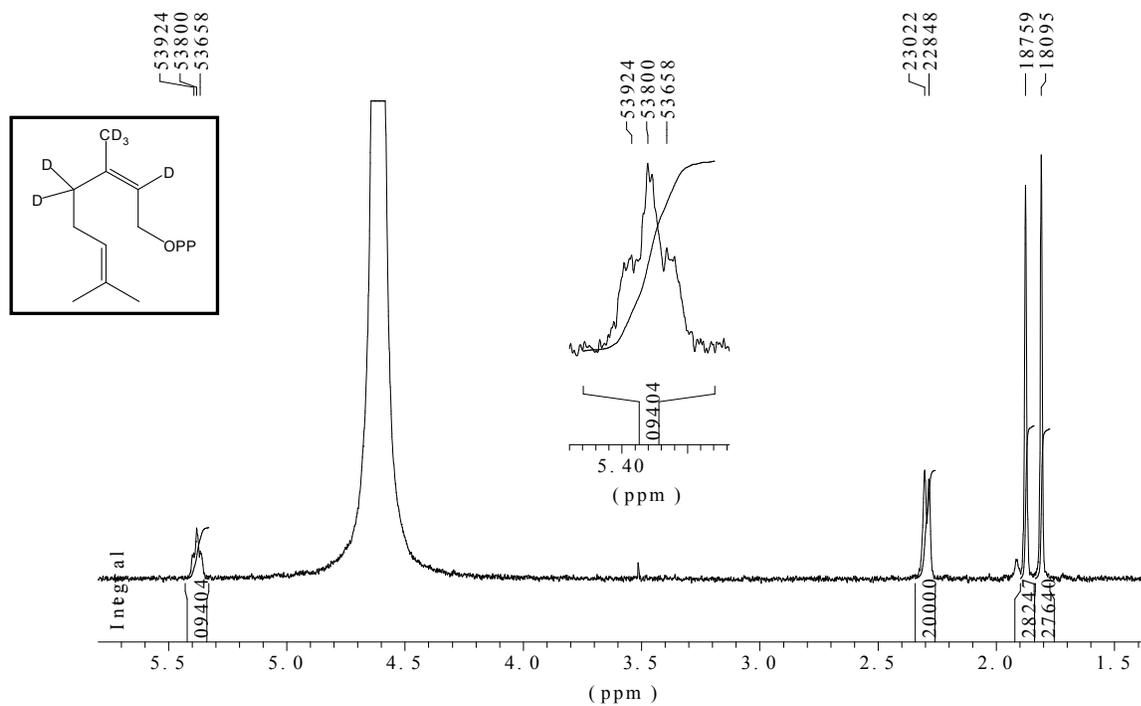
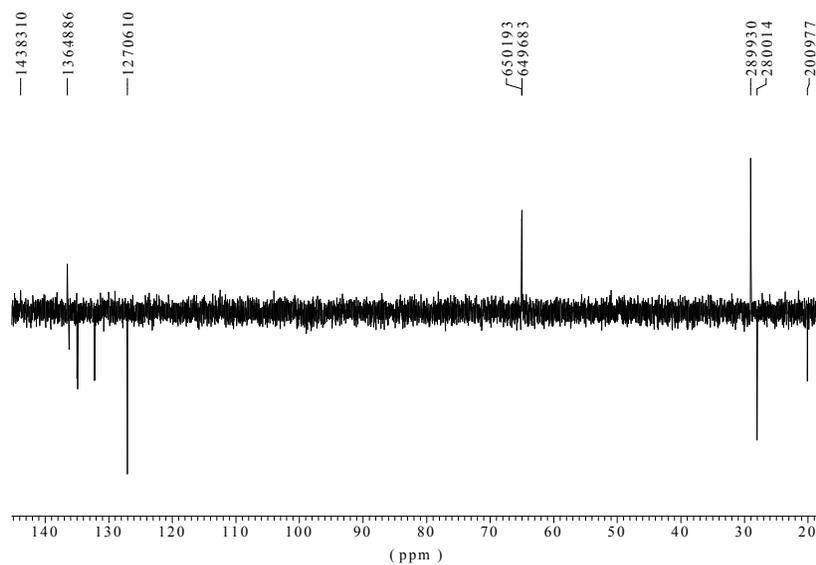
**$^1\text{H}$  NMR of (2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dien-1-ol (8b)** **$^{13}\text{C}$  NMR of (2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dien-1-ol (8b)**

**$^1\text{H}$  NMR of (2Z,6E)-[2- $^2\text{H}$ ]-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (8c)** **$^{13}\text{C}$  NMR of (2Z,6E)-[2- $^2\text{H}$ ]-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (8c)**

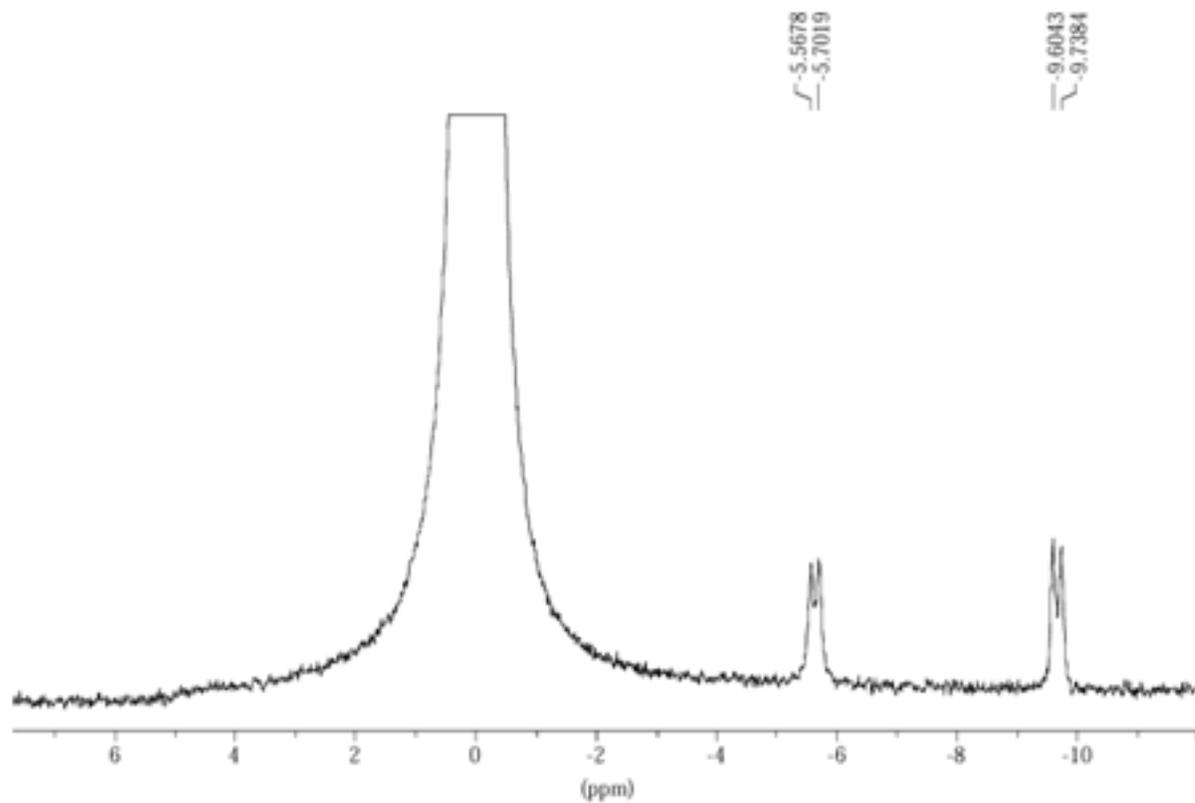
**$^1\text{H}$  NMR of (2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (8d)** **$^{13}\text{C}$  NMR of (2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (8d)**

**$^1\text{H}$  NMR of Trisammonium (2Z)-[2- $^2\text{H}$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate (2a)** **$^{13}\text{C}$  NMR of Trisammonium (2Z)-[2- $^2\text{H}$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate (2a)**

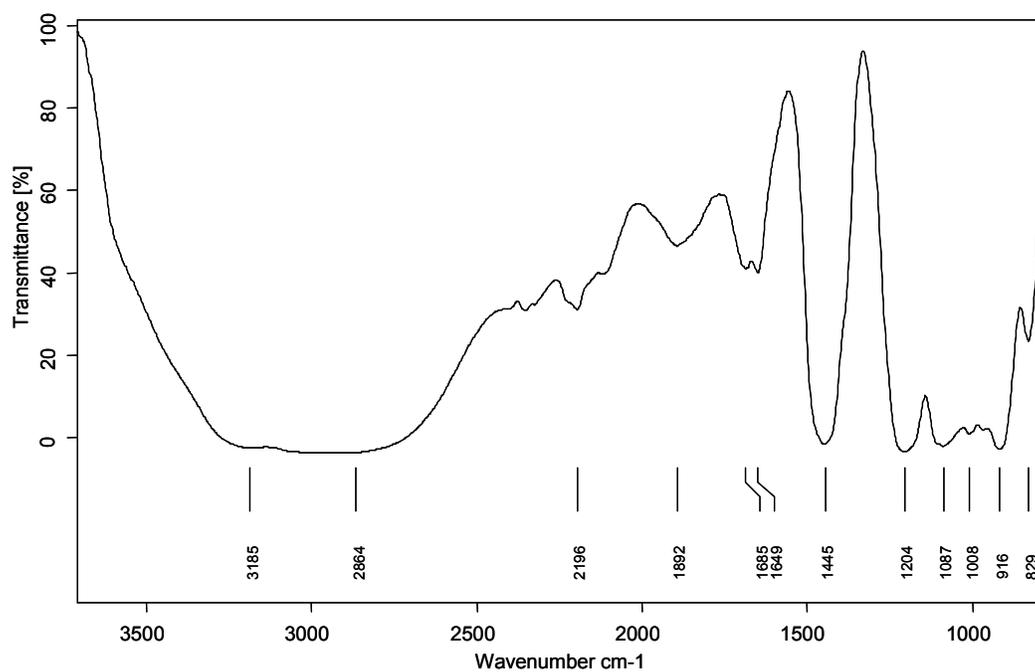
**$^{31}\text{P}$  NMR of Trisammonium (2Z)-[2- $^2\text{H}$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate (2a)****IR of Trisammonium (2Z)-[2- $^2\text{H}$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate (2a)**

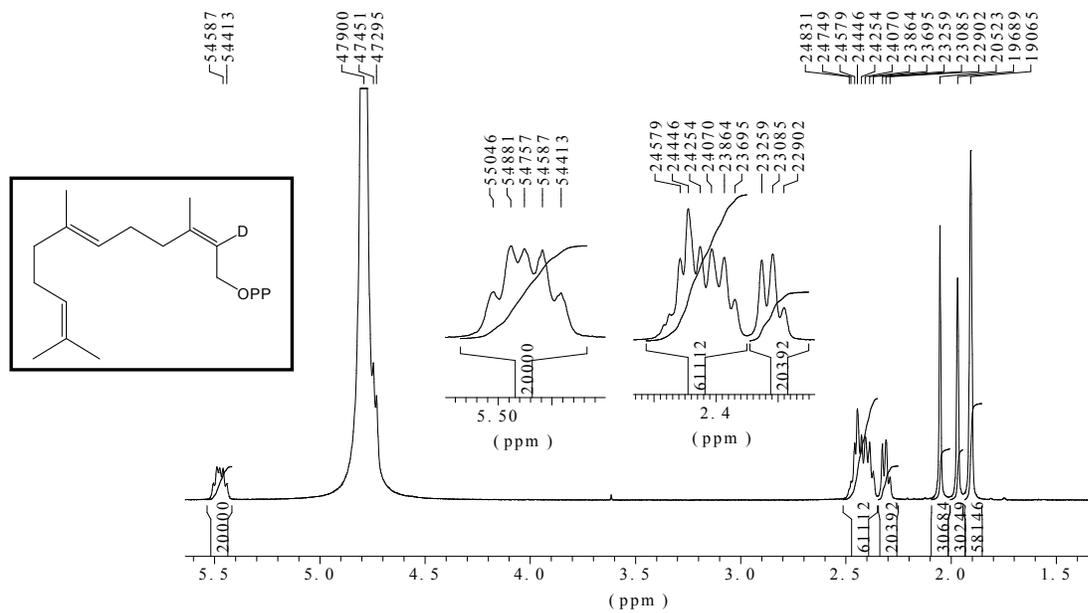
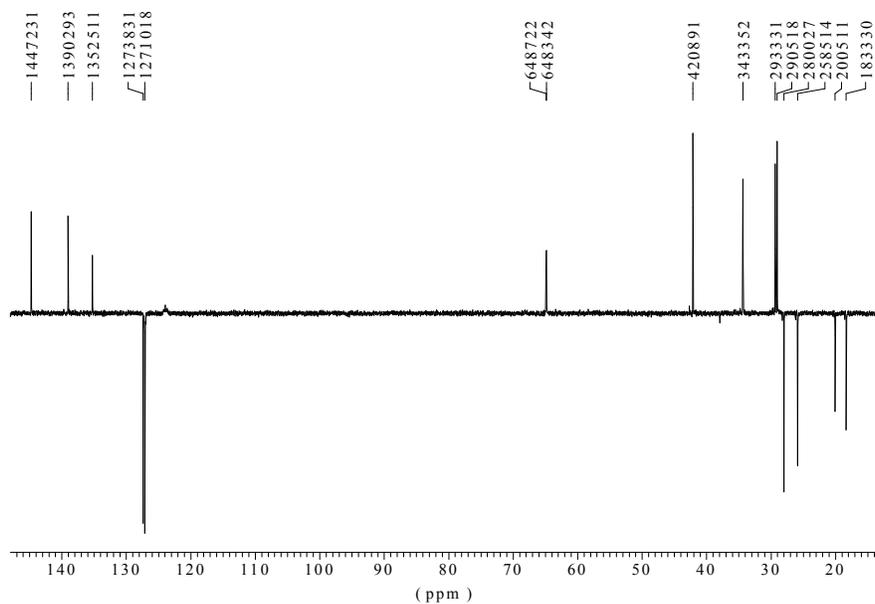
**$^1\text{H}$  NMR of Trisammonium (2*Z*)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate****(2b)** **$^{13}\text{C}$  NMR of Trisammonium (2*Z*)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dienyl****Diphosphate (2b)**

**$^{31}\text{P}$  NMR of Trisammonium (2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate (2b)**

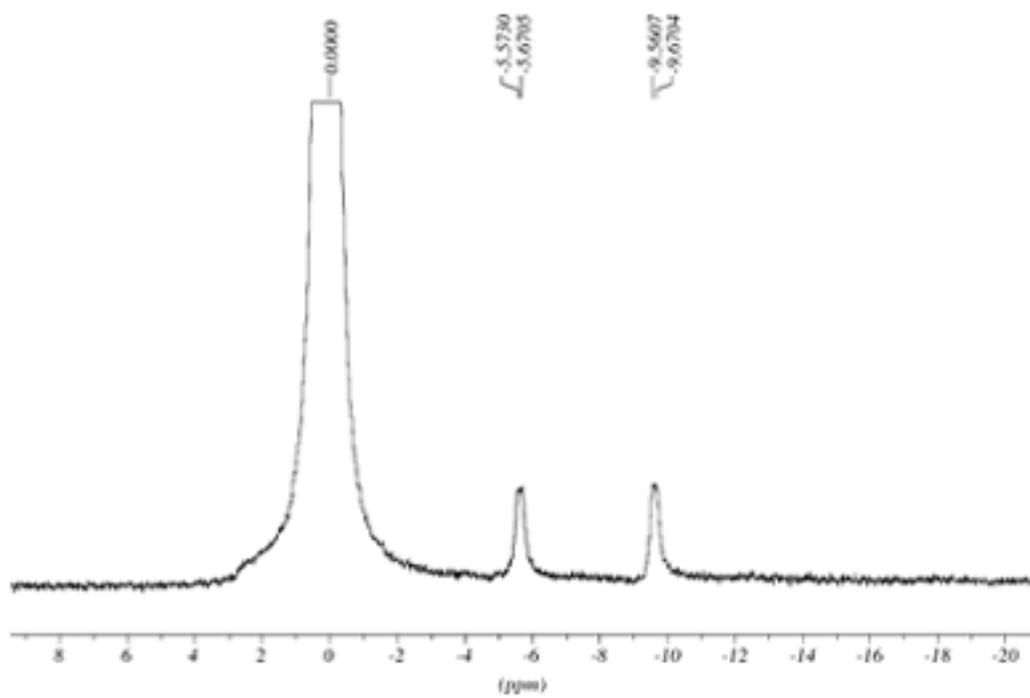


**IR of Trisammonium (2Z)-[2,4,4,9,9,9- $^2\text{H}_6$ ]-3,7-Dimethylocta-2,6-dienyl Diphosphate (2b)**

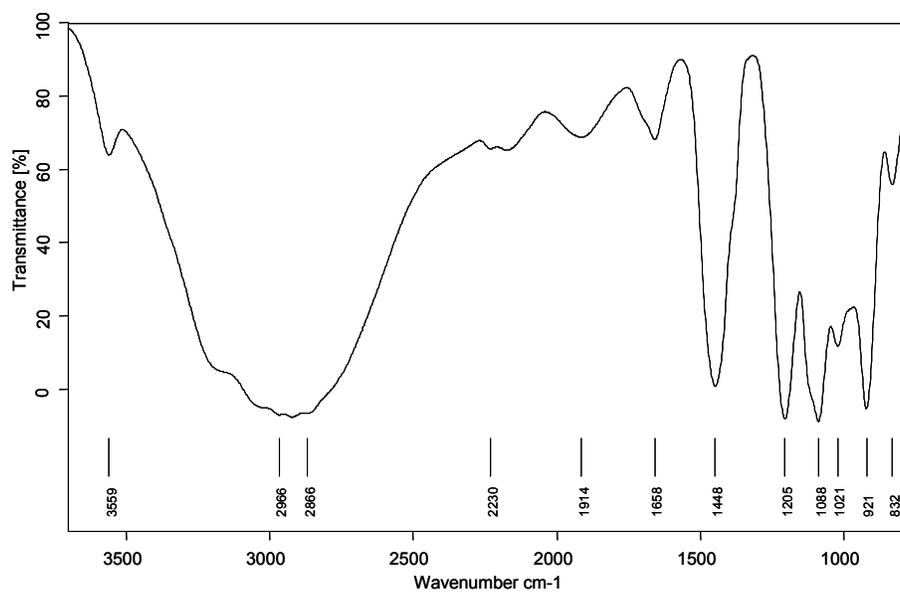


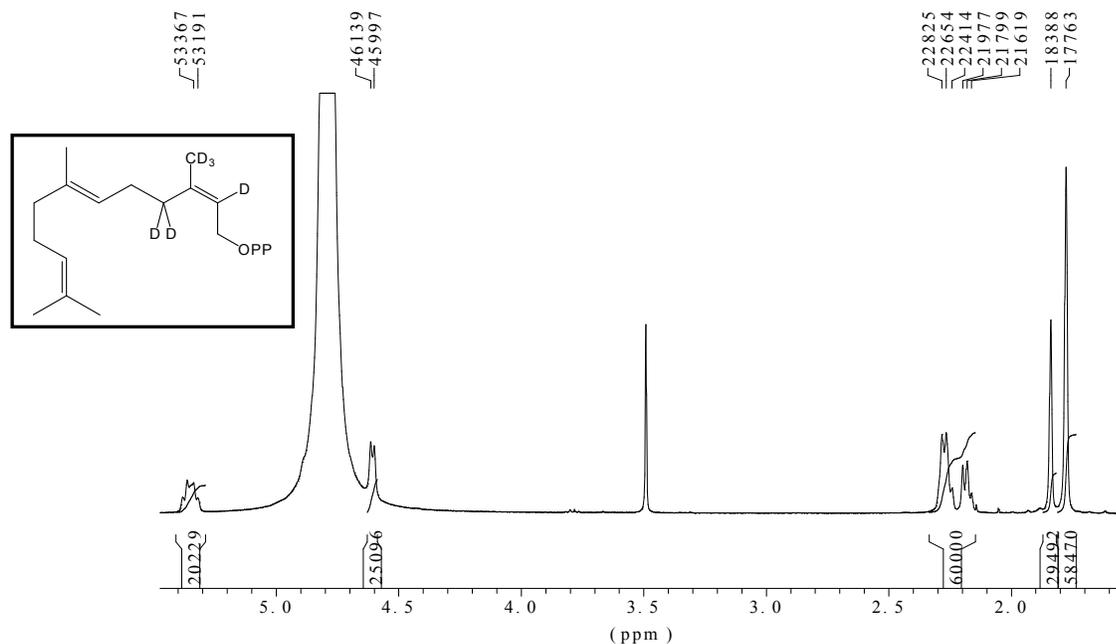
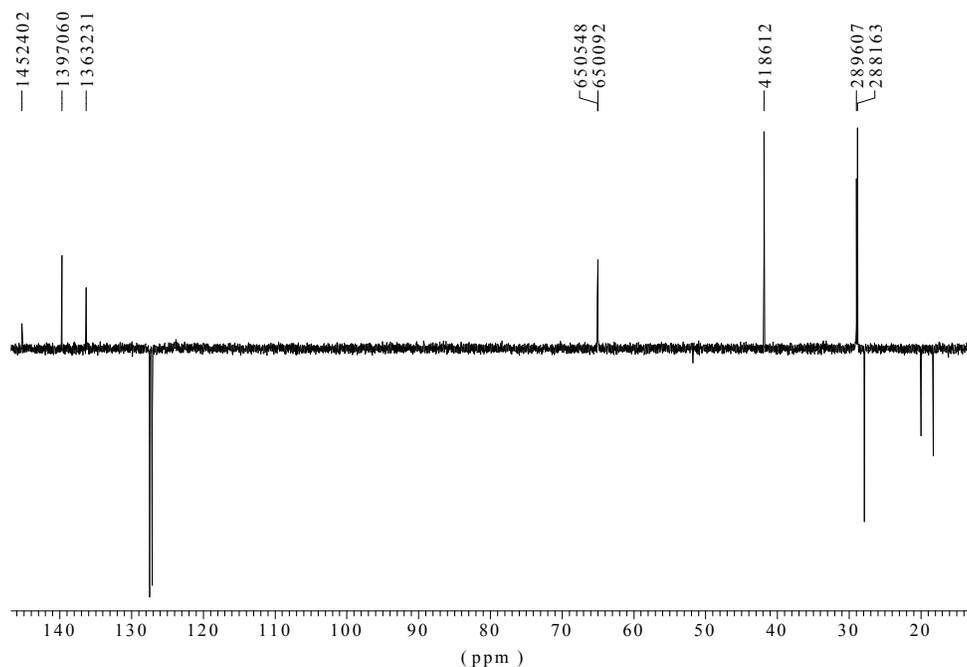
**$^1\text{H}$  NMR of Trisammonium (2*Z*,6*E*)-[2- $^2\text{H}$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl****Diphosphate (2c)** **$^{13}\text{C}$  NMR of Trisammonium (2*Z*,6*E*)-[2- $^2\text{H}$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl****Diphosphate (2c)**

**$^{31}\text{P}$  NMR of Trisammonium (2*Z*,6*E*)-[2- $^2\text{H}$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl Diphosphate (2c)**

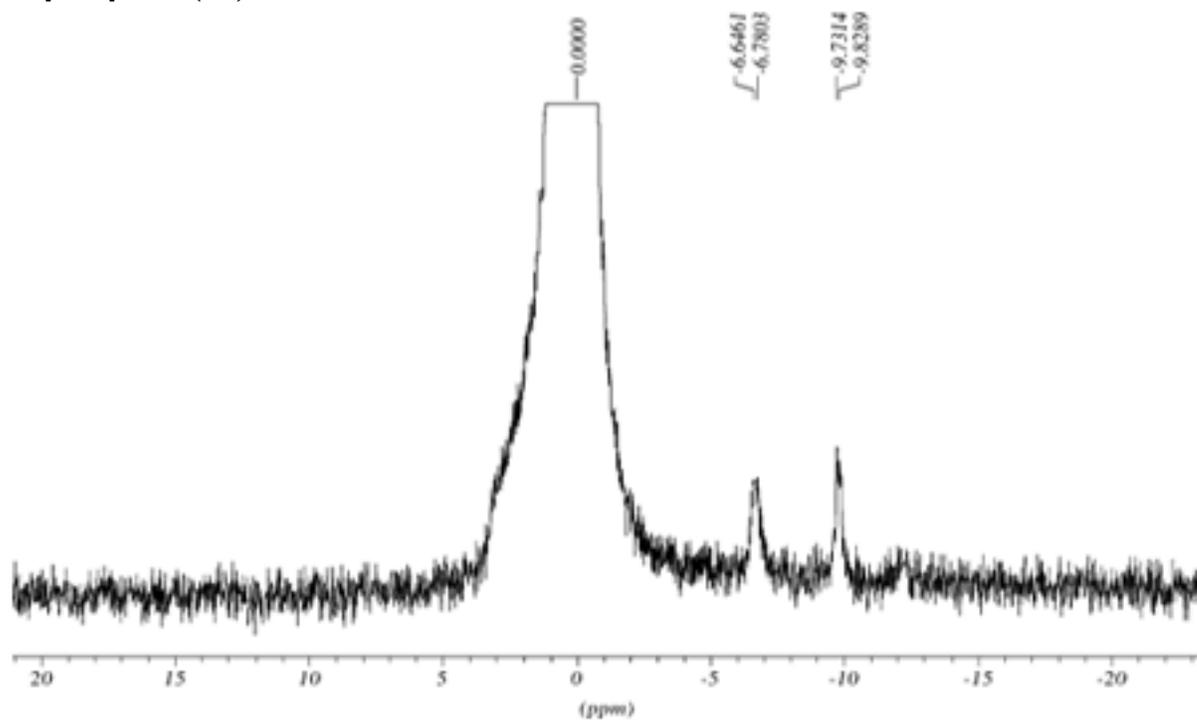


**IR of Trisammonium (2*Z*,6*E*)-[2- $^2\text{H}$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl Diphosphate (2c)**

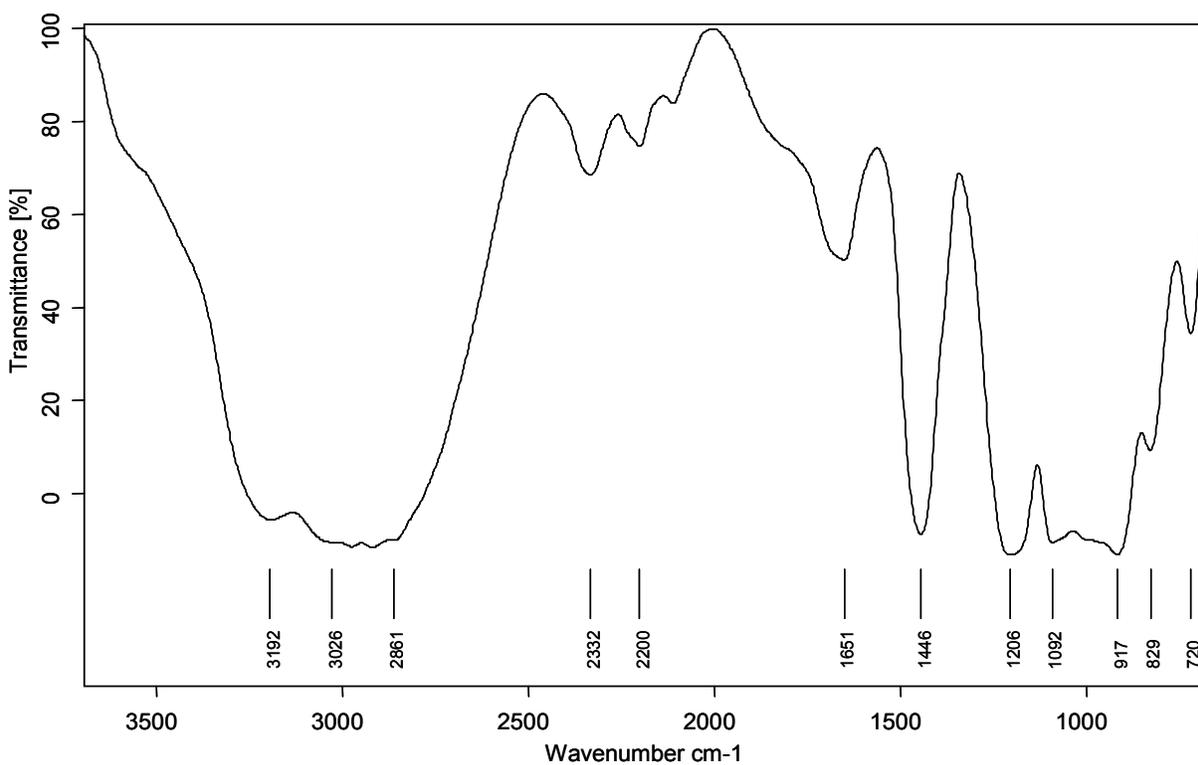


**$^1\text{H}$  NMR of Trisammonium (2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl Diposphate (2d)** **$^{13}\text{C}$  NMR of Trisammonium (2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl Diposphate (2d)**

**$^{31}\text{P}$  NMR of Trisammonium (2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl Diphosphate (2d)**



**IR of Trisammonium (2Z,6E)-[2,4,4,13,13,13- $^2\text{H}_6$ ]-3,7,11-Trimethyldodeca-2,6,10-trienyl Diphosphate (2d)**



- 1 N. Gatto, A. Vattekkatte, T. Kollner, J. Degenhardt, J. Gershenzon and W. Boland, *Chem Commun (Camb)*, 2015, **51**, 3797.
- 2 T. G. Köllner, C. Schnee, J. Gershenzon and J. Degenhardt, *Plant Cell*, 2004, **16**, 1115.