Reinvestigation of the Substitutions Reaction of Stereogenic Phosphoryl Compounds: Stereochemistry, Mechanism and Applications

Li-Juan Liu[a‡], Wei-Min Wang[a‡], Lan Yao[a‡], Fan-Jie Meng[a], Yong-Ming Sun[a], Hao Xu[a], Zhong-Yuan Xu[a], Qiang Li[a], Chang-Qiu Zhao[a]* and Li-Biao Han[b]*

[a:] College of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng, Shandong 252059, China

[b:] National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan

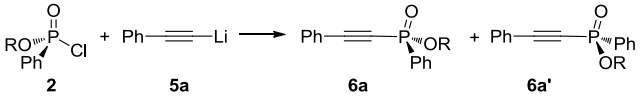
Contents

Part 1. The substitution of P-Cl bond with alkynyl metallic reagents.

Typical procedure for the reaction of 2 with 5a:

The powder of **2** (0.046 g, 0.147 mmol) was added portionwise within 1 minute to the solution of **3a** that was prepared in situ from addition of *n*BuLi (1.6 M solution in hexane, 0.092 ml, 0.147 mmol) to the solution of phenylethyne (0.016 ml, 0.147 mmol) in ether (1 ml) at 0 ℃. Then the mixture was stirred for about 3 h while the temperature elevated to room temperature gradually. Saturated ammonium chloride solution was added, and the mixture was extracted with dichloromethane for three times. The combined organic layer was dried over sodium sulfate, concentrated in vacuo. The residue was used for analysis with NMR. The yields and diastereomeric ratio were estimated by $^{31}P\{^{1}H\}$-NMR spectroscopy based on **2**.

Table S1. Reaction of 2 with 5a under various conditions



R = (-)-Menthyl

Entry	Temperature/Time	Yield % (**6a**/**6a'**) (**2**/**2'**) [a]
1	0 ℃ to rt/3 h	>99 (89:11) [b]
2	0 ℃ to rt/4 h	80 (99: 1)
3	0 ℃/1 h	96 (68:32) [c]
4	rt/4 h	95 (53:47)
5	–80 ℃/1 h; to rt/16 h	96 (45:55) [c,d]
6	–20 ℃/5 min; to rt/5 h	>99 (70:30) [c, d]
7	–20 ℃/1 h; to rt/16 h	91 (40:60) [d]
8	–20 ℃/9 h; rt/1 h	99 (42: 58)
9	–20 ℃/9 h; rt/16 h	99 (40: 60)
10	–20 ℃/9 h	97 (51:49) [e]
11	–45 ℃/8 h	99 (>99:1)
12	–15 ℃/2.5 h; rt/5 min	99 (51:49) [f]
13	0 ℃/20 min; rt /2.5 h	37 (69:31) (68:32) [c, g]
14	–15 ℃ /3 h; rt/5 min	63 (80:20) (81:19) [g]
15	–15 ℃ /3 h; rt/16 h	64 (83:17) (50:50) [g]
16	–20 ℃ /3 h; rt/5 min	61 (62:38) (91:9) [g]

[a] In a typical procedure, the powder of **2** was added portionwise within 1 minute to the solution of **5a**. The yields and dr were estimated by the peaks' integrations on ^{31}P and proton NMR spectroscopy. The data in second parentheses was the ratio of unconsumed **2/2'** (if applicable). [b] **5a** was added to the solution of **2** (0.147 M in ether). [c] Solid of **2** added in one portion. [d] The mixture was warmed from an ice-water bath to rt. [e] The mixture was quenched with acetic acid at –20 ℃. [f] Both two reactants were used in 0.0735 M solution of ether. [g] The ratio of **5a**/**2** was 1:2.

A diastereomeric mixture of (S_P)-**2**/ (R_P)-**2'** reacted with phenylethynyl lithium **5a**, affording two stereoisomers of *O*-menthyl phenyl (phenylethynyl) phosphinate **6a** and **6a'** whose ^{31}P-NMR signals were observed at 7.78 (s) and 9.37 ppm (s), respectively. The yield and dr (ratio of **6a**/**6a'**) for the reaction of optically pure (S_P)-**2** with **5a** under various conditions were examined (Table S-1). When **2** was slowly added to **5a** at 0 ℃, **6a** was formed with greater than 99:1 dr. The

reverse addition resulted in poor dr (entries 1–3), which indicated the dr was sensitive to the stoichiometry of the two starting materials. In entries 1 to 11, a temperature dependence of the dr was observed. When the reaction was carried out at either rt or −20 °C (entries 4 to 10), poor dr was obtained. When **2** and **5a** were mixed at −80 °C, then gradually warmed to rt, **6a**/**6a'** were still formed with poor dr (entry 5), in contrast to the normal thinking that better selectivity is obtained at low temperature, as seen in Imamoto's reaction at −78 °C. However, when **2** and **5a** were stirred at −45 °C for enough time (8 h), **6a** was formed in near quantitative conversion and >99 : 1 dr (entry 11).

After **2** and **5a** were mixed at –80 ℃ in ether, the solution was monitored with ^{31}P-NMR spectral. At beginning stage at rt, only the peak of **6a** was observed. The peaks of unconsumed **2**, its epimer **2'**, **6a'** and other *P*-containing species were not detected. The peak of **6a'** started to emerge after five minutes, and gradually increased with prolonged time, until 59:41 dr after an hour (Figure S-1).

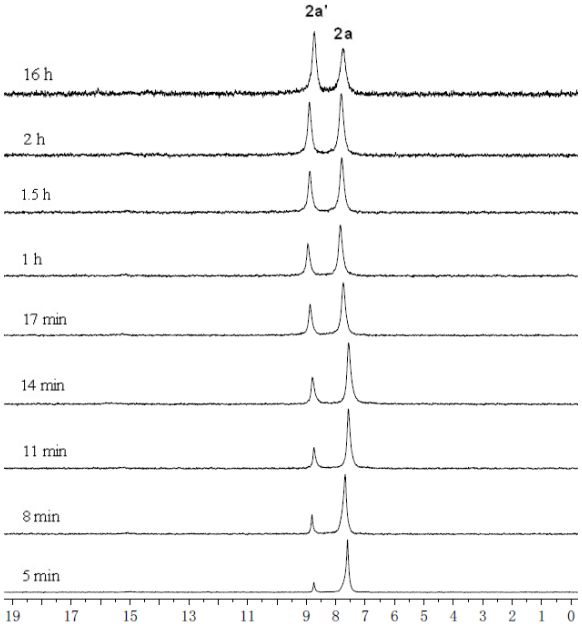
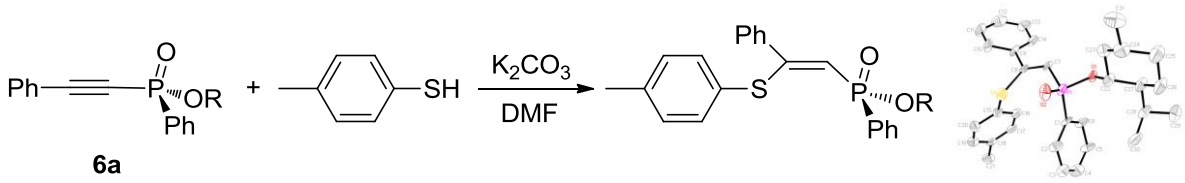


Figure S1. Relationship between the formation of **6a**/**6a'** and the reaction time (in ether).

In dilute solution, **6a'** was not dominantly formed (entry 12). The results indicated a dilute solution, which was developed after formation of **6a**, was not favour for the formation of **6a'**. **6a'** was not produced from the reported chloride-exchange or epimerization of **1**, as proved by no epimerization of **1** was observed in the LiCl-containing solution.

The reaction of 4-methylbenzenethiol with **6a** under alkali condition to afford menthyl (*Z*)-2-(*p*-tolylthio)-2-phenylvinyl (phenyl)phosphinate, whose S_P configuration was confirmed by X-ray diffraction (Scheme S-1). Because the addition didn't involve in phosphorus atom, the phosphorus atom of **6a** has the same R_P configuration. On the basis of the above observations, two routes to form **6a** and **6a'** were proposed as *P*-inversed normal S_N2 substitution (route A, to form **6a**) and *P*-retained Berry pseudorotation (BPR, route B, to form **6a'**), respectively.



R = (-)-Menthyl

Scheme S1. The conversion of 6a and the confirmation of its structure.

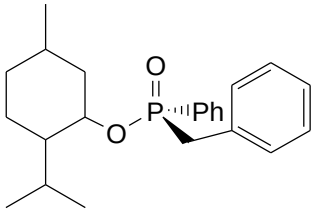
Part 2. The comparison of ^{31}P NMR spectroscopy for 12 and 12'

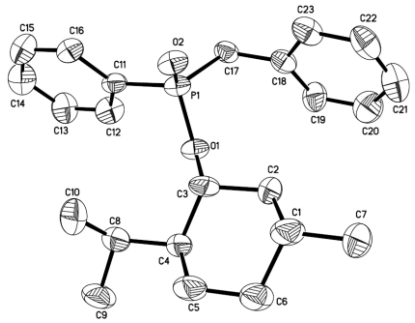
Table S2. The comparison of ^{31}P-NMR spectrum for the R_P/S_P-12/12'.

entry	R/major product	**(S_P)-12** ^{31}P-NMR spectrum (ppm):	**(R_P)-12'** ^{31}P-NMR spectrum (ppm):
1	Me (**12a**)	40.74 (s, 90 %)	40.05 (s, 10 %).
2	Et (**12b**)	45.19 (s, 98 %)	44.20 (s, 2 %).
3	*n*-Bu (**12c**)	43.97 (s, 98 %)	43.05 (s, 2%).
4	*i*-Pr (**12d**)	47.70.	
5	*cyclo*-Hex (**12e**)	44.96.	
6	*s*-Bu (**12f**)	47.17 and 46.79 (two single peaks, 88.5%)	45.86 and 45.62 (two single peaks, 11.5%)
7	*t*-Bu (**12g**)	48.98.	
8	Bn (**12h**)	38.41.	
9	allyl (**12i**)	39.02 (s, 98 %)	38.47 (s, 2 %)
10	*p*-BrC_6H_4 (**12j**)	(R_P) 28.96.	
11	*p*-ClC_6H_4 (**12k**)	(R_P) 28.84	
12	**12k/12k'**(from **2/2'**)	(R_P) 29.000	(S_P) 28.955
13	*o*-MeC_6H_4 (**12l**)	(R_P) 25.67	
14	**12m**	(R_P) 28.84	
15	Me (**12a'**)		40.41
16	Et (**12b'**)		44.20.
17	*n*-Bu (**12c'**)		42.99.
18	*i*-Pr (**12d'**)	47.61 (s, 3%)	δ 46.41 (s, 97%),
19	*s*-Bu (**12f'**)	47.32 and 46.94 (two single peaks, 11%)	45.98 and 45.75 (two single peaks, 89%).
20	*t*-Bu (**12g'**)	48.99 (s, 13%)	48.19 (s, 87%),
21	Bn (**12h'**)		37.63
22	allyl (**12i'**)	39.08 (s, 4%)	38.53 (s, 96%).
23	*p*-BrC_6H_4 (**12j'**)	(R_P) 29.075 (s, 12%)	(S_P) 29.036 (s, 88%).
34	*o*-MeC_6H_4 (**12l'**)		(S_P) 29.02.
25	*p*-MeC_6H_4 (**12n'**)		(S_P) 29.30.

Part 3. Crystallography information.

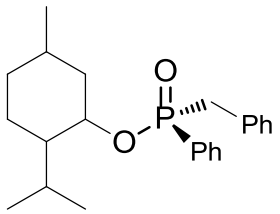
Table S3. Crystallography data of (S_P)-*O*-Menthyl benzylphenylphosphinate (12h) (ORTEP drawing of 12h with thermal ellipsoids at the 30% probability)

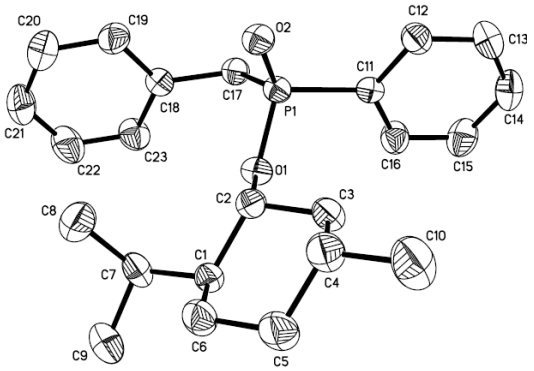




Empirical formula	C_{23} H_{31} N O_2 P
Crystal system	Orthorhombic
Space group	P2 (1)2 (1)2 (1)
Formula weight	370.45
a, Å	5.7278 (6)
b, Å	17.5633 (19)
c, Å	21.791 (2)
α, deg	90
β, deg	90
γ, deg	90
V, Å3	2192.2 (4)
Z	4
T, K	298 (2)
λ, Å	0.71073
ρ, g cm−3	1.122
Rint	0.1094
R1 [I N 2σ (I)]	0.0522
R1 (all data)	0.1436
wR2 [I N 2σ (I)]	0.1184
wR2 (all data)	0.1655
Flack	0.0 (2)
CCDC Number	1526361

Table S4. Crystallography data of (R_P)-*O*-Menthyl benzylphenylphosphinate (12h') (ORTEP drawing of 12h' with thermal ellipsoids at the 30% probability)

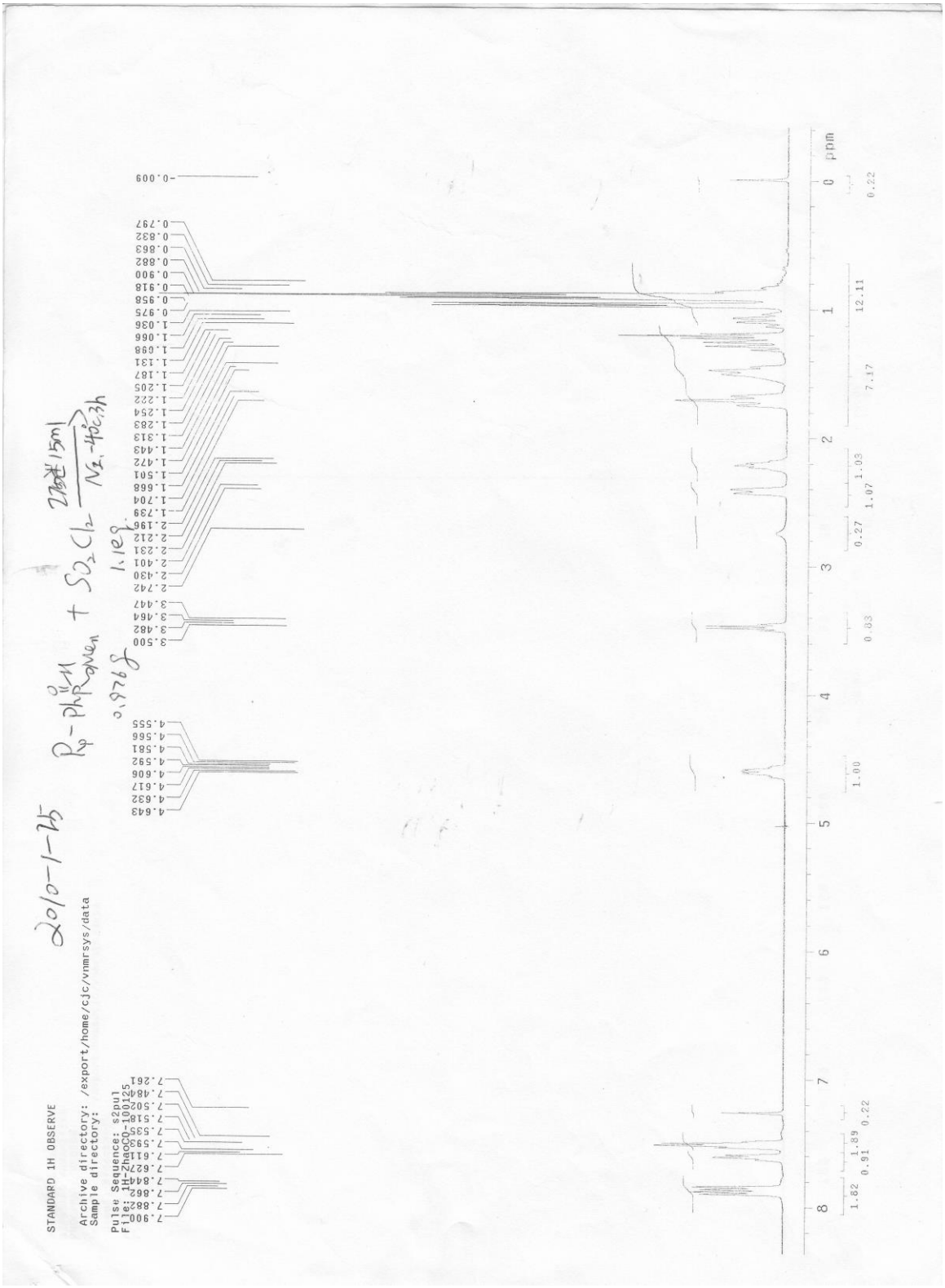




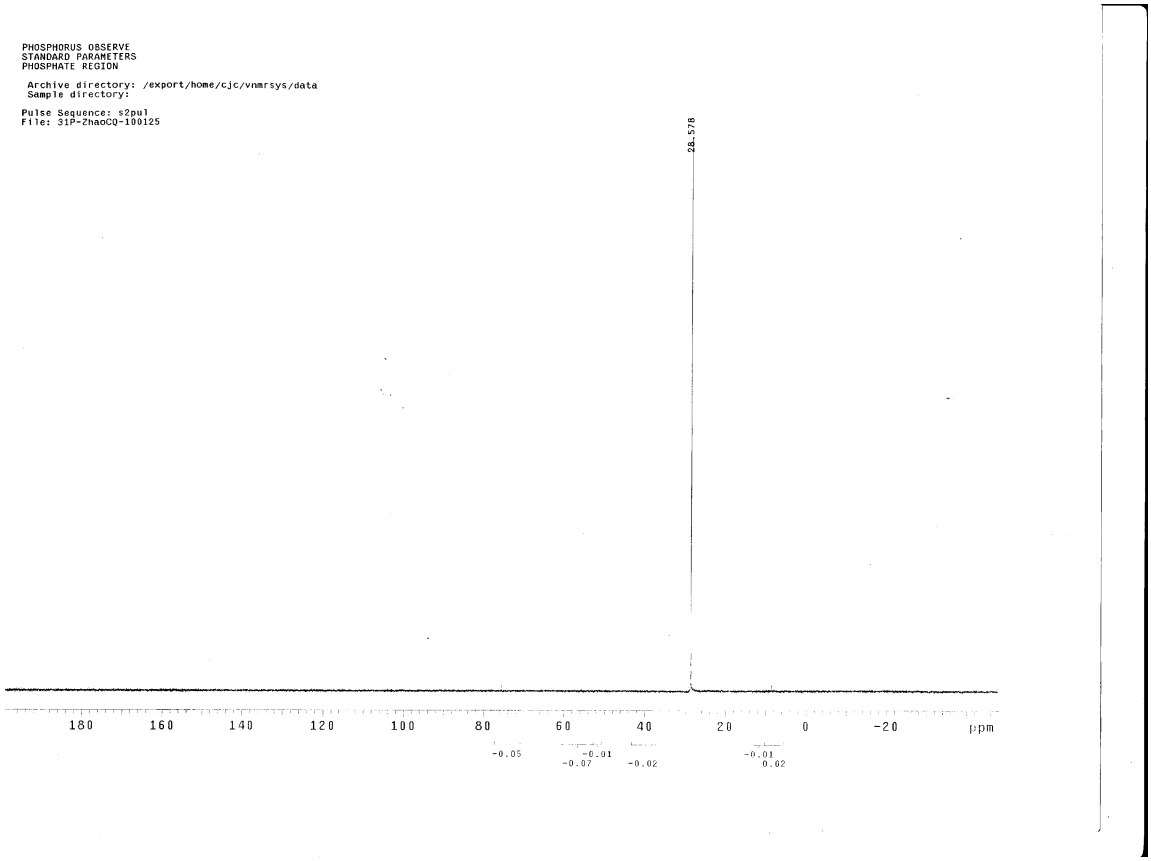
Empirical formula	$C_{23}\ H_{31}\ N\ O_2\ P$
Crystal system	Monoclinic
Space group	P2 (1)
Formula weight	370.45
a, Å	12.4777 (11)
b, Å	5.7970 (7)
c, Å	15.4190 (19)
α, deg	90
β, deg	100.7270 (10)
γ, deg	90
V, Å3	1095.8 (2)
Z	2
T, K	298 (2)
λ, Å	0.71073
ρ, g cm−3	1.123
Rint	0.0846
R1 [I N 2σ (I)]	0.0658
R1 (all data)	0.0877
wR2 [I N 2σ (I)]	0.1567
wR2 (all data)	0.1697
Flack	-0.17 (16)
CCDC Number	1526362

Part 4. Selected ^{1}H, ^{31}P and ^{13}C NMR spectroscopy

(S_P)-*O*-Menthyl phenylphosphonochloridate 2



(S_P)-*O*-Menthyl phenylphosphonochloridate 2



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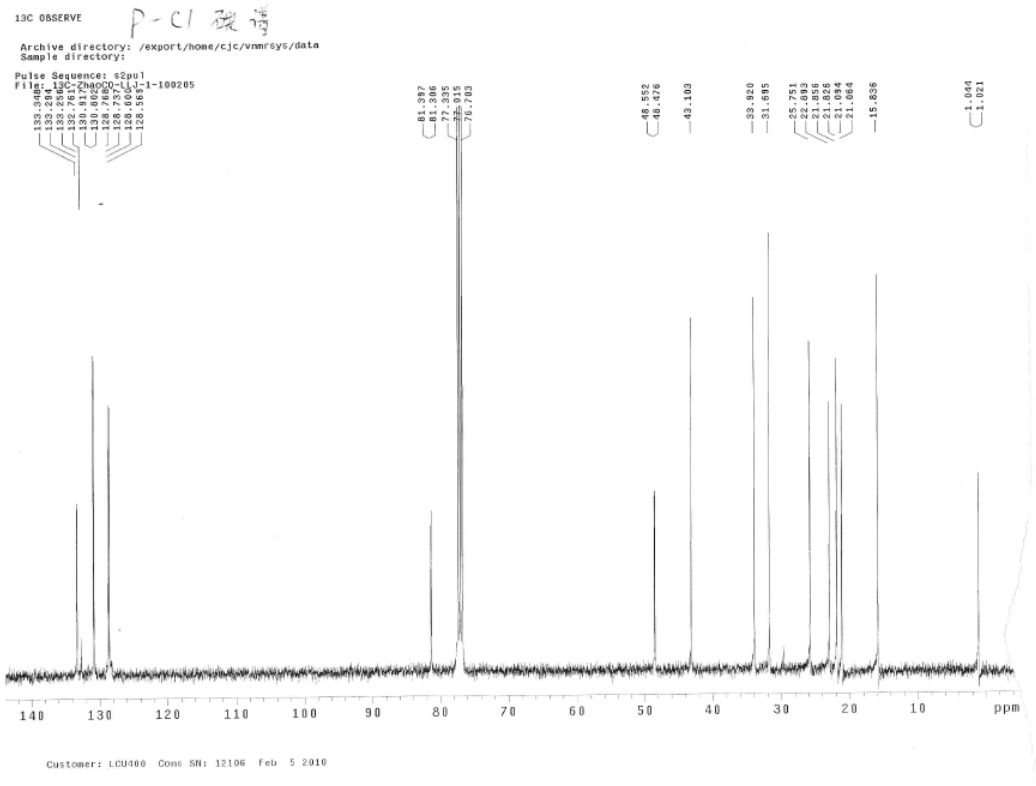
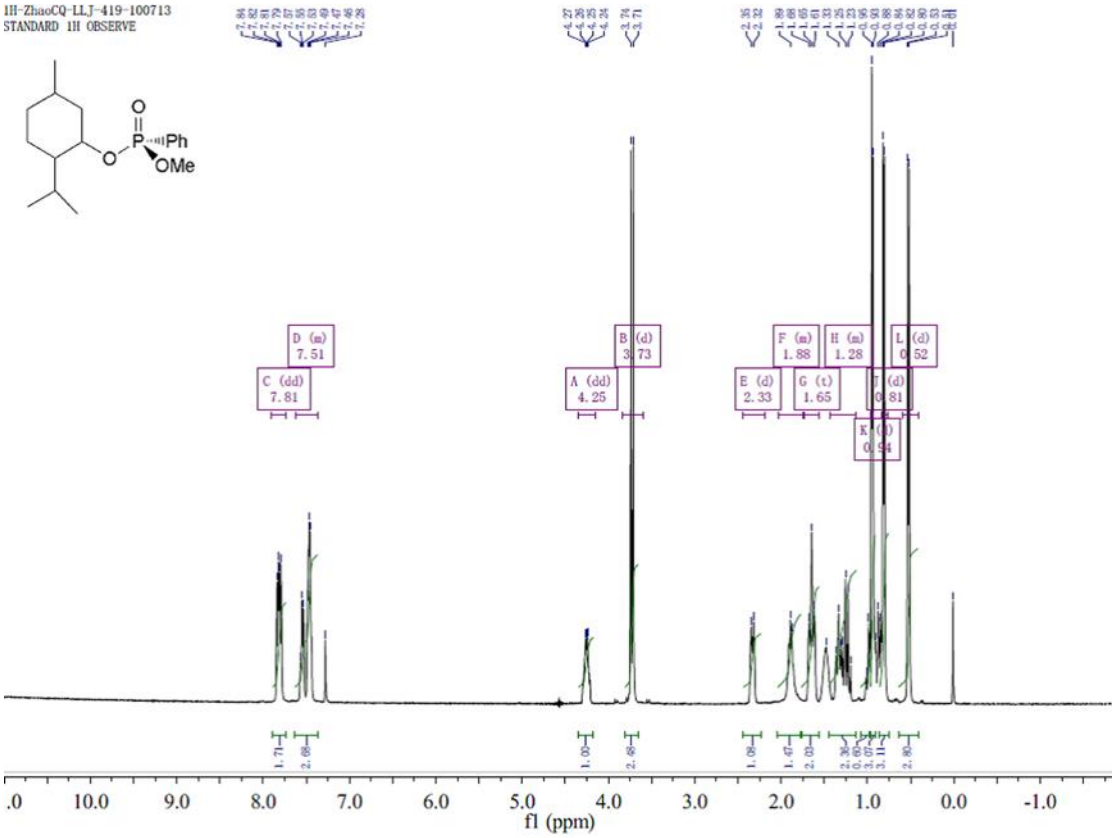
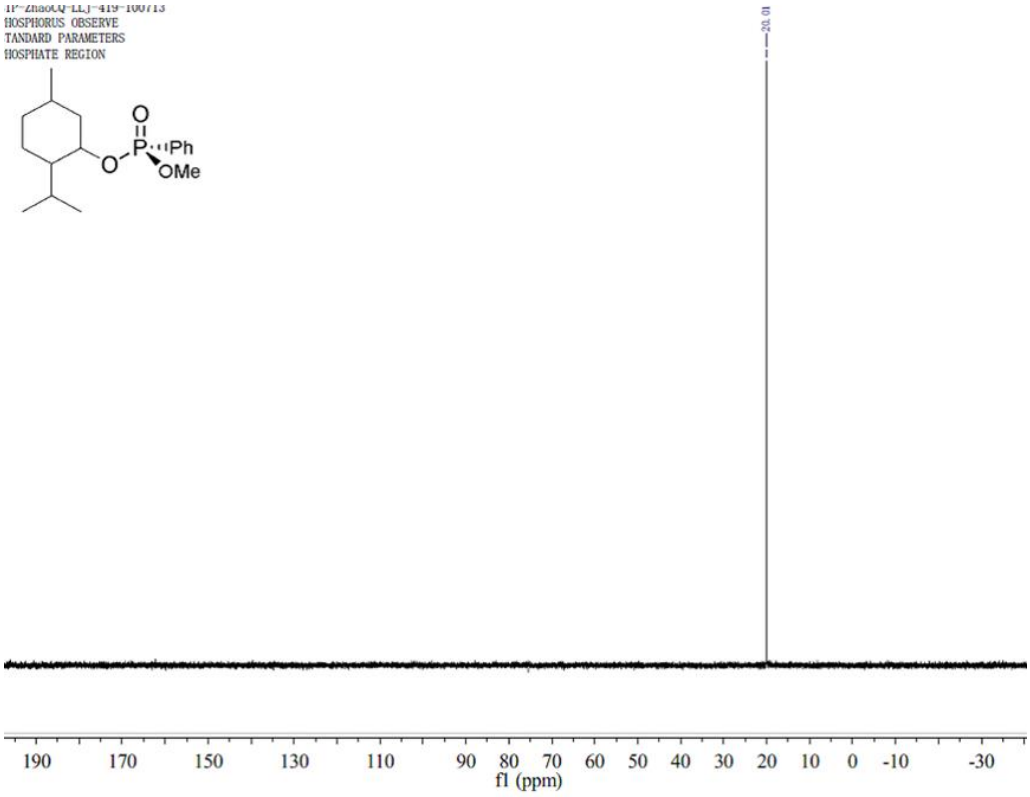


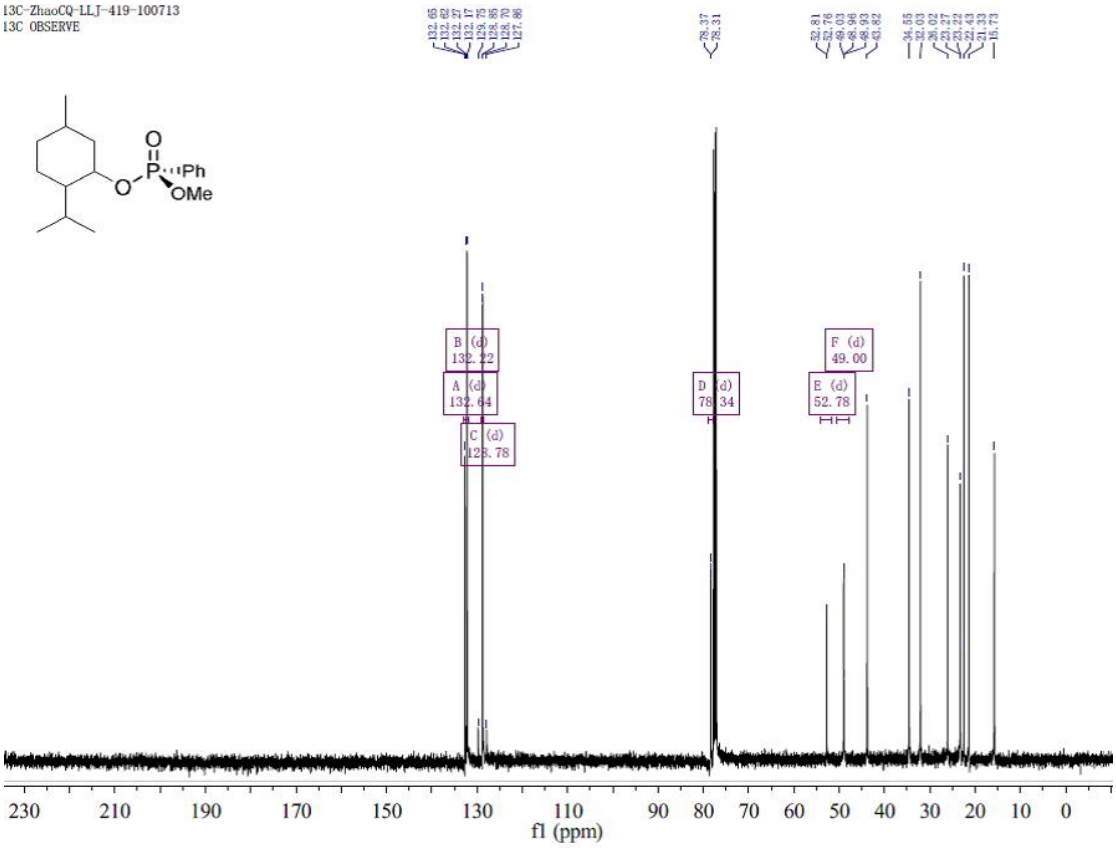
(S_P)-*O*-Methyl *O*-menthyl phenylphsophinate 3



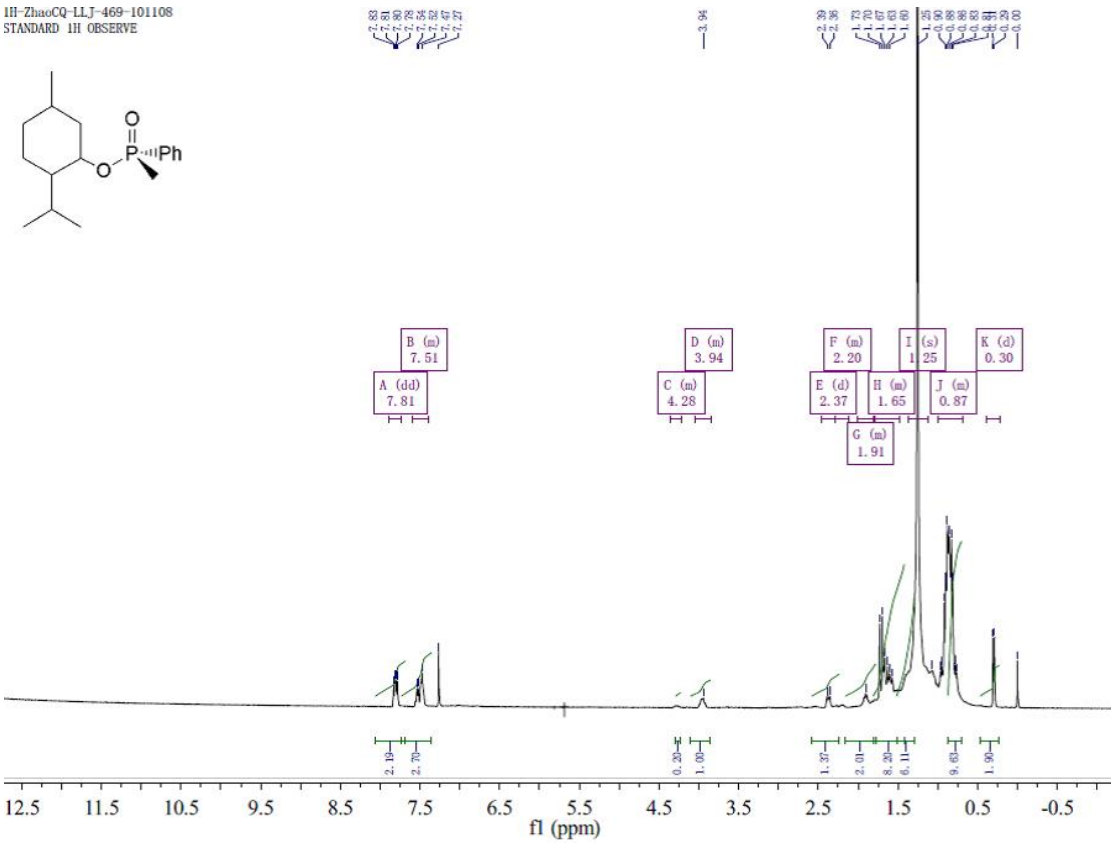
(S_P)-*O*-Methyl *O*-menthyl phenylphsophinate 3



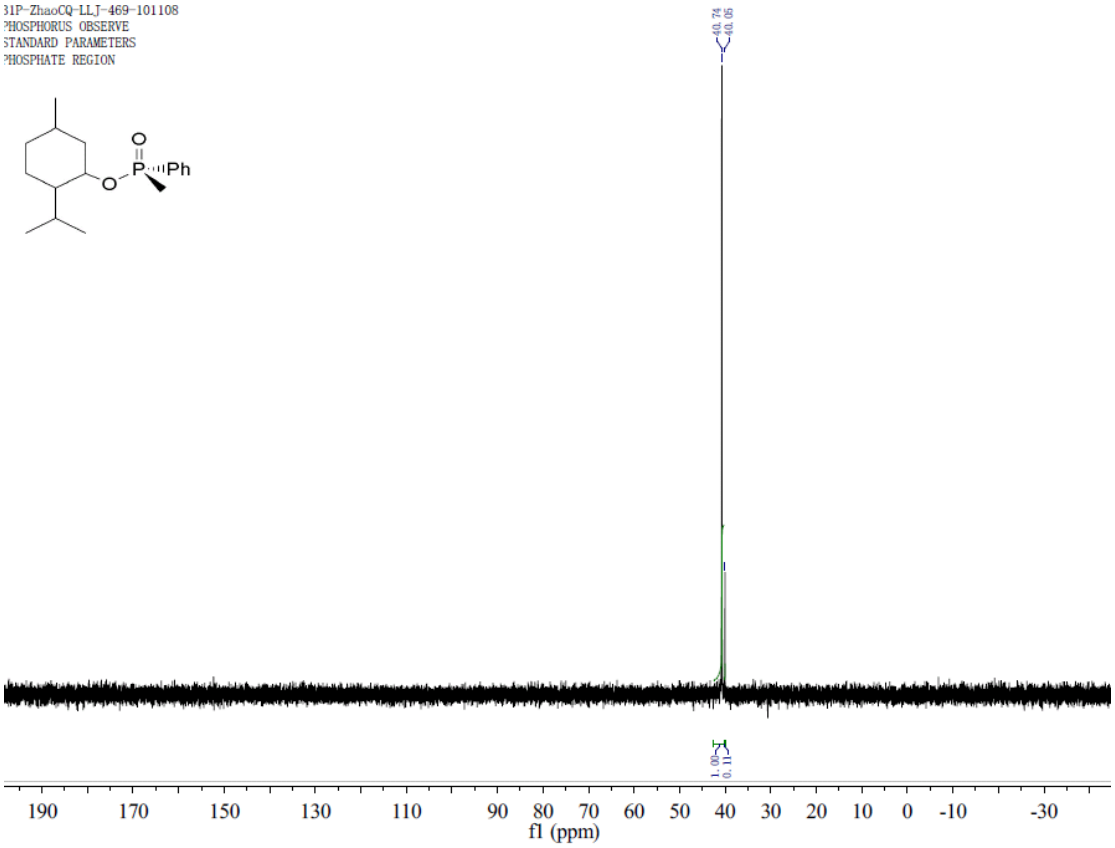
(S_P)-*O*-Methyl *O*-menthyl phenylphsophinate 3



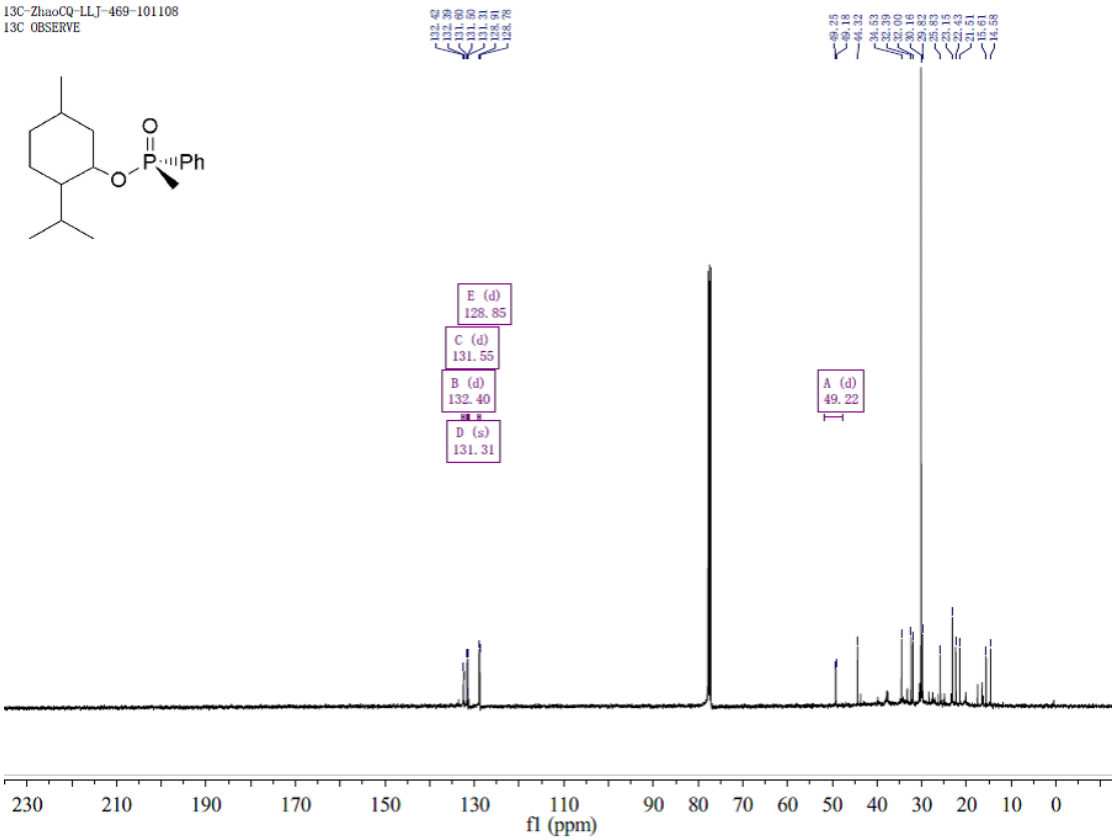
(S_P)-*O*-Menthyl methylphenylphosphinate (12a)



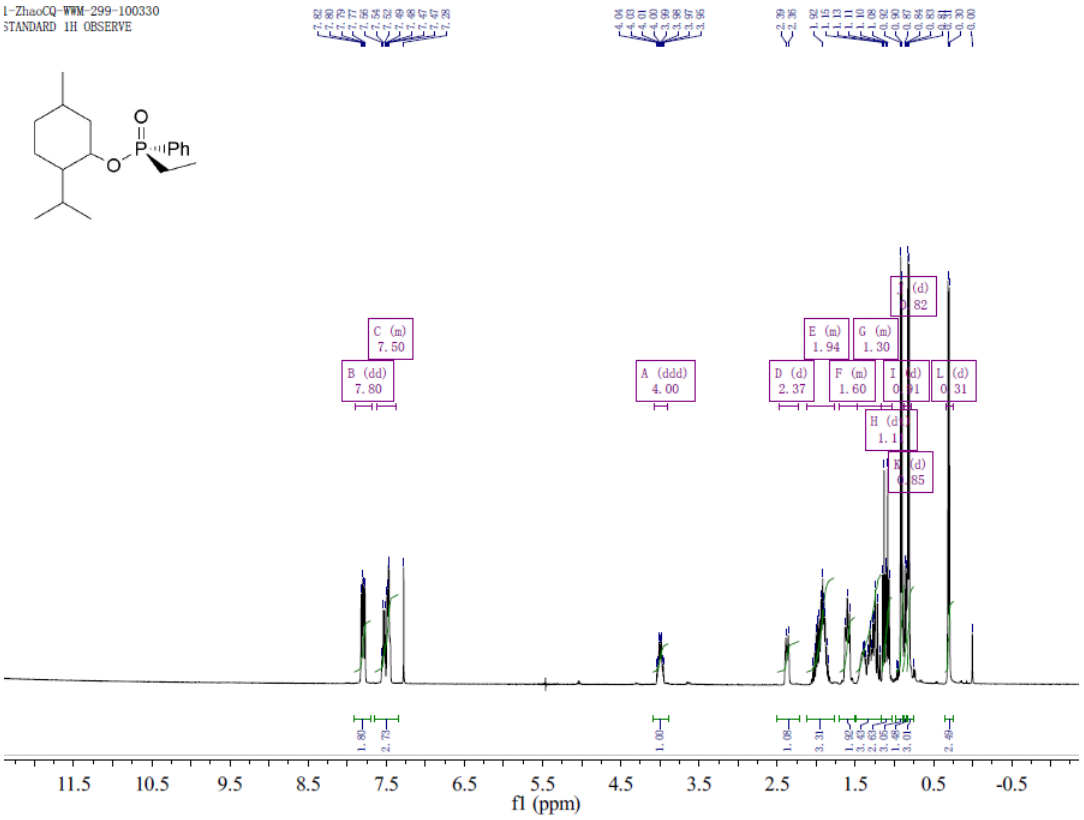
(S_P)-*O*-Menthyl methylphenylphosphinate (12a)



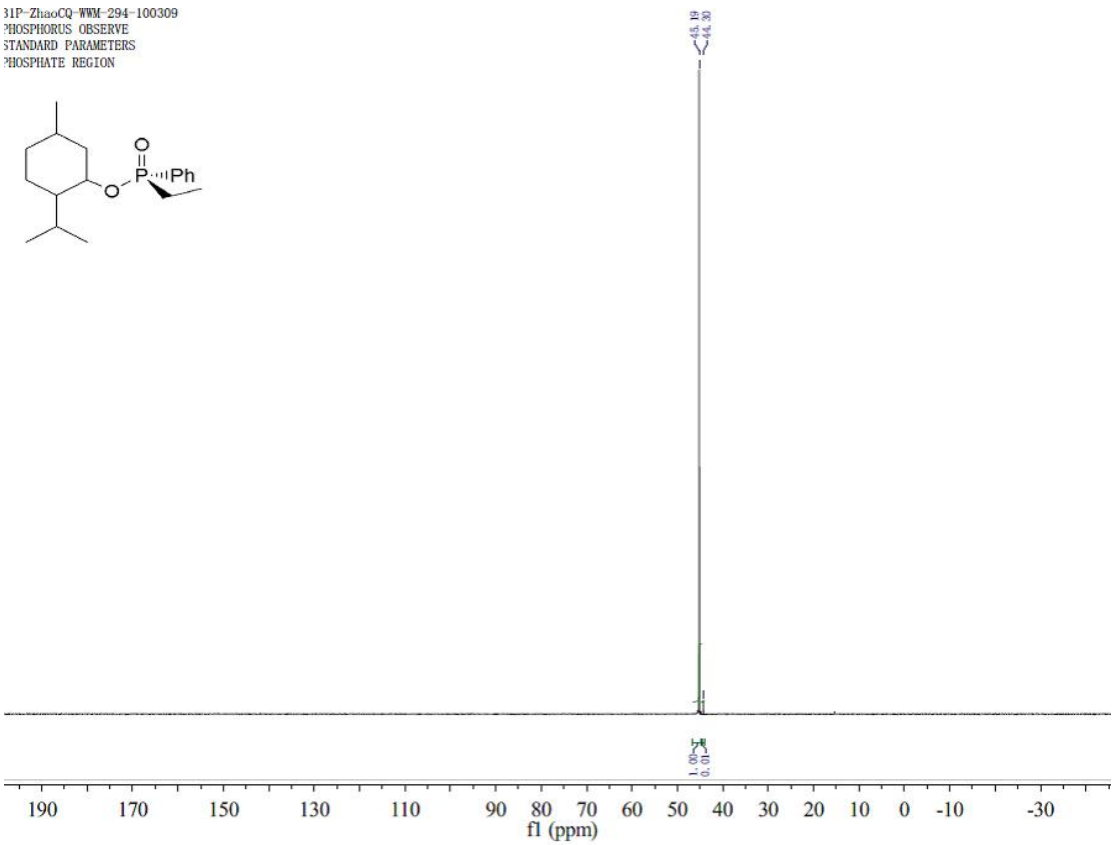
(S_P)-*O*-Menthyl methylphenylphosphinate (12a)



(S_P)-*O*-Menthyl ethylphenylphosphinate (12b)



(S_P)-*O*-Menthyl ethylphenylphosphinate (12b)



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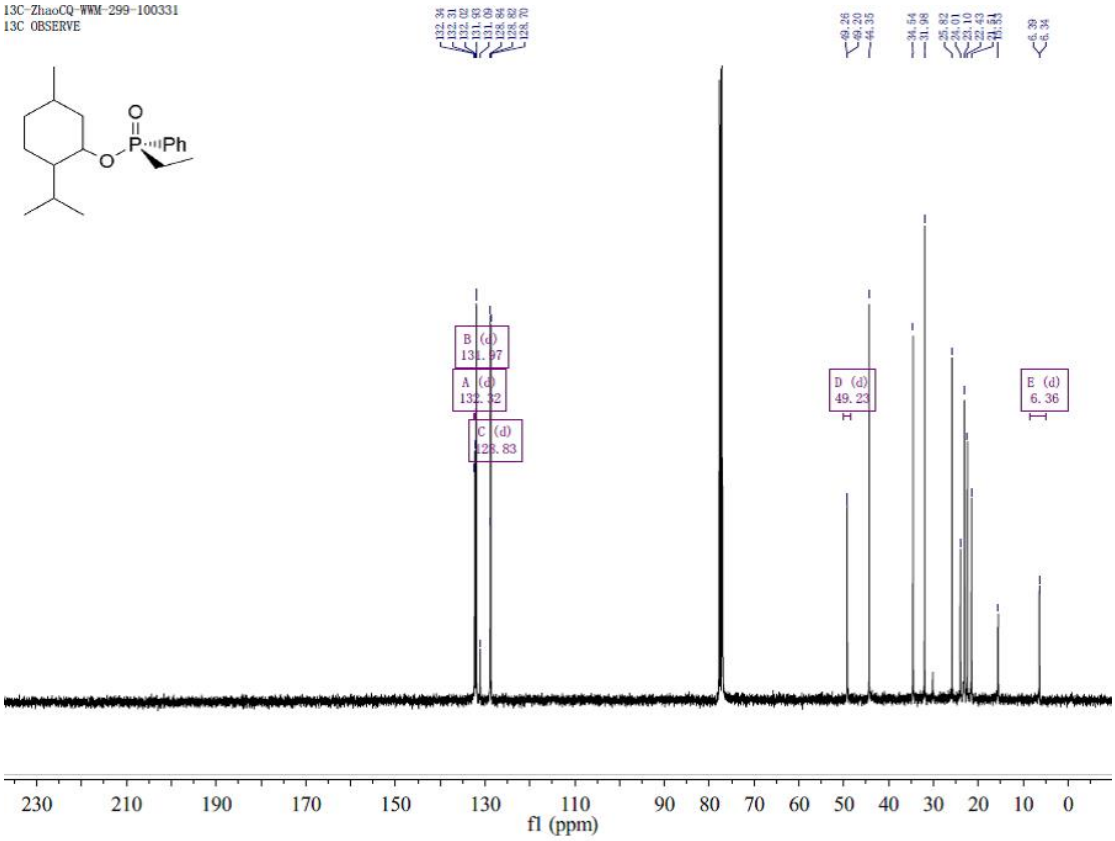
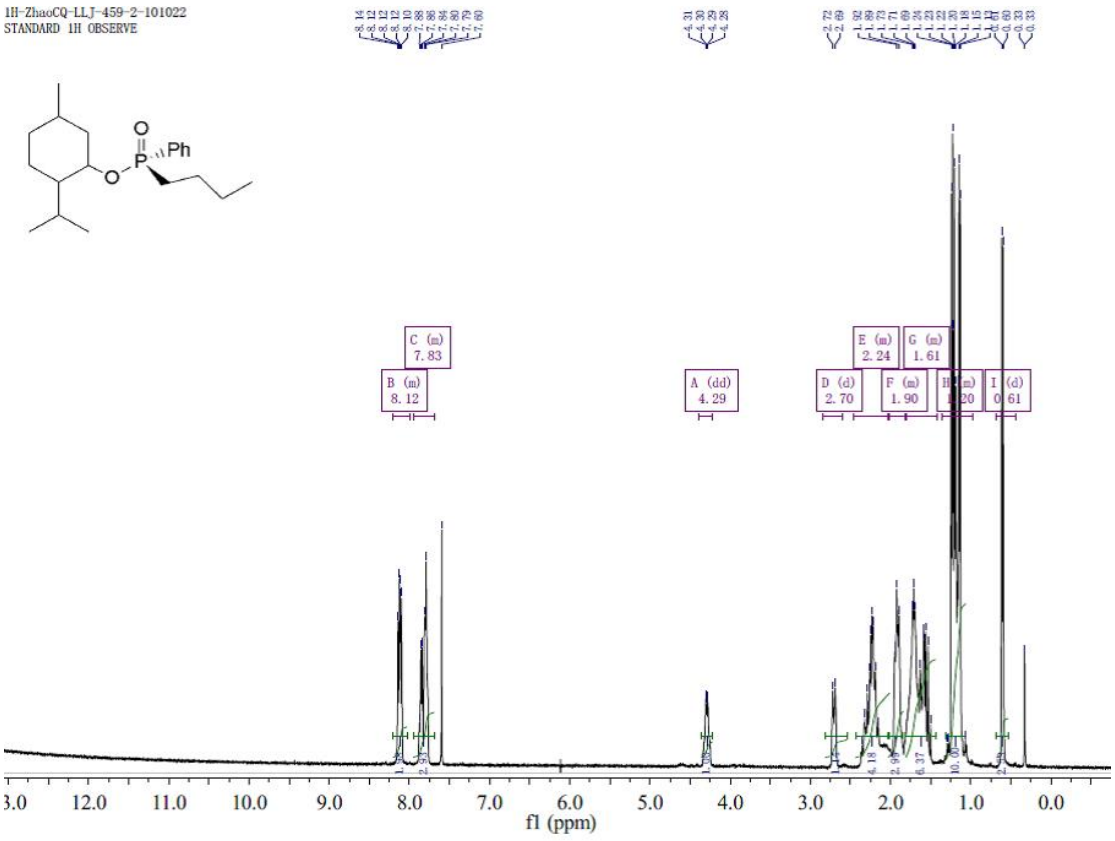
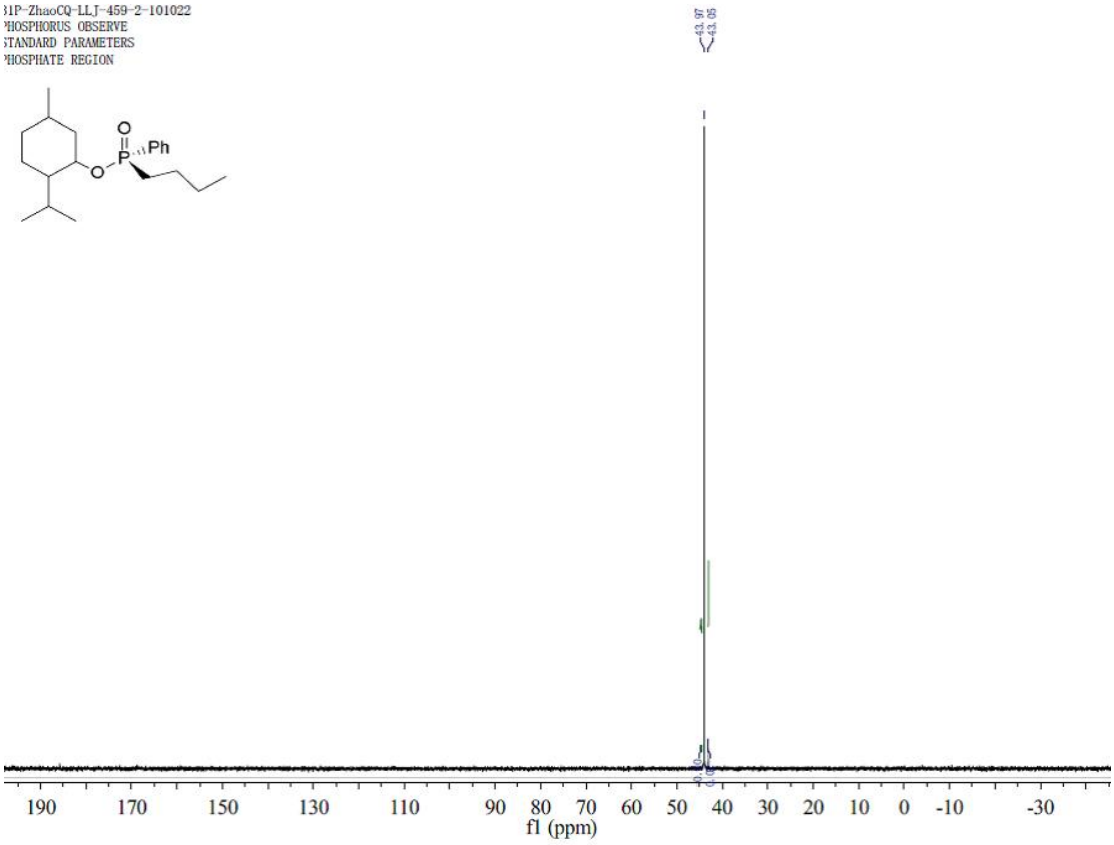


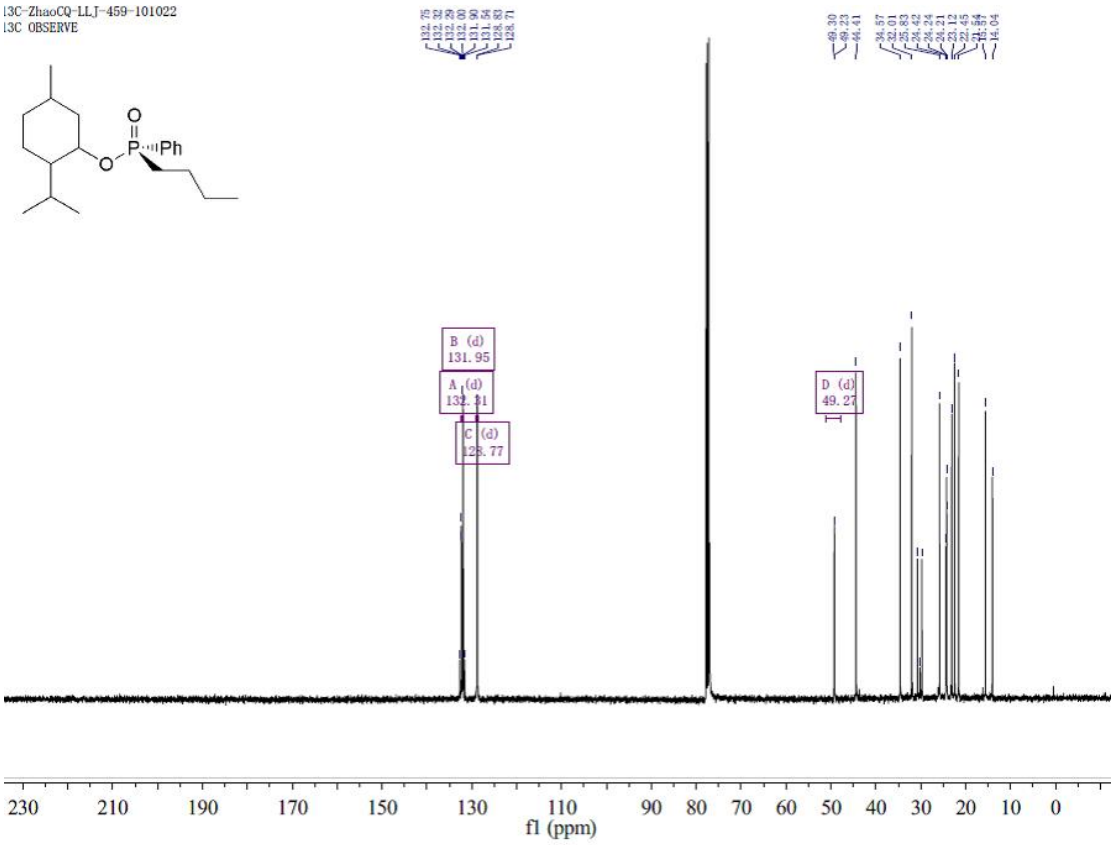
(S_P)-*O*-Menthyl *n*-butylphenylphosphinate (12c)



(S_P)-*O*-Menthyl *n*-butylphenylphosphinate (12c)



(S_P)-*O*-Menthyl *n*-butylphenylphosphinate (12c)



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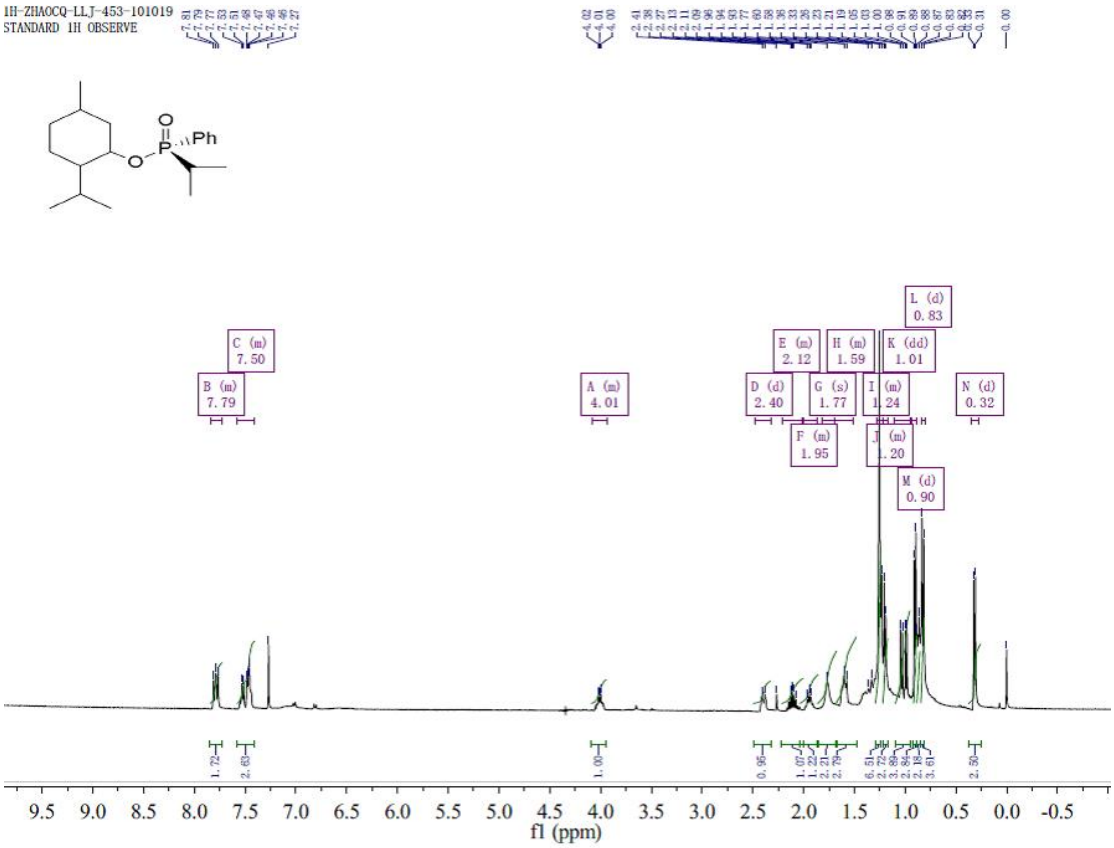

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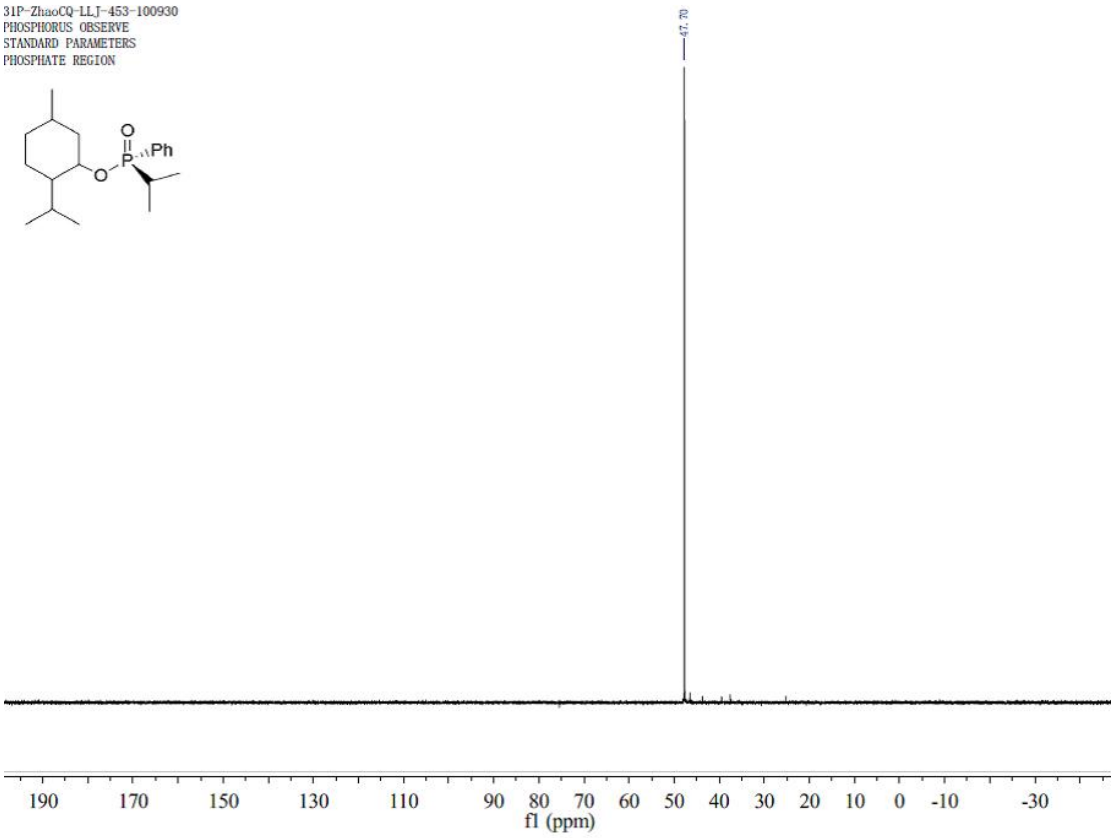
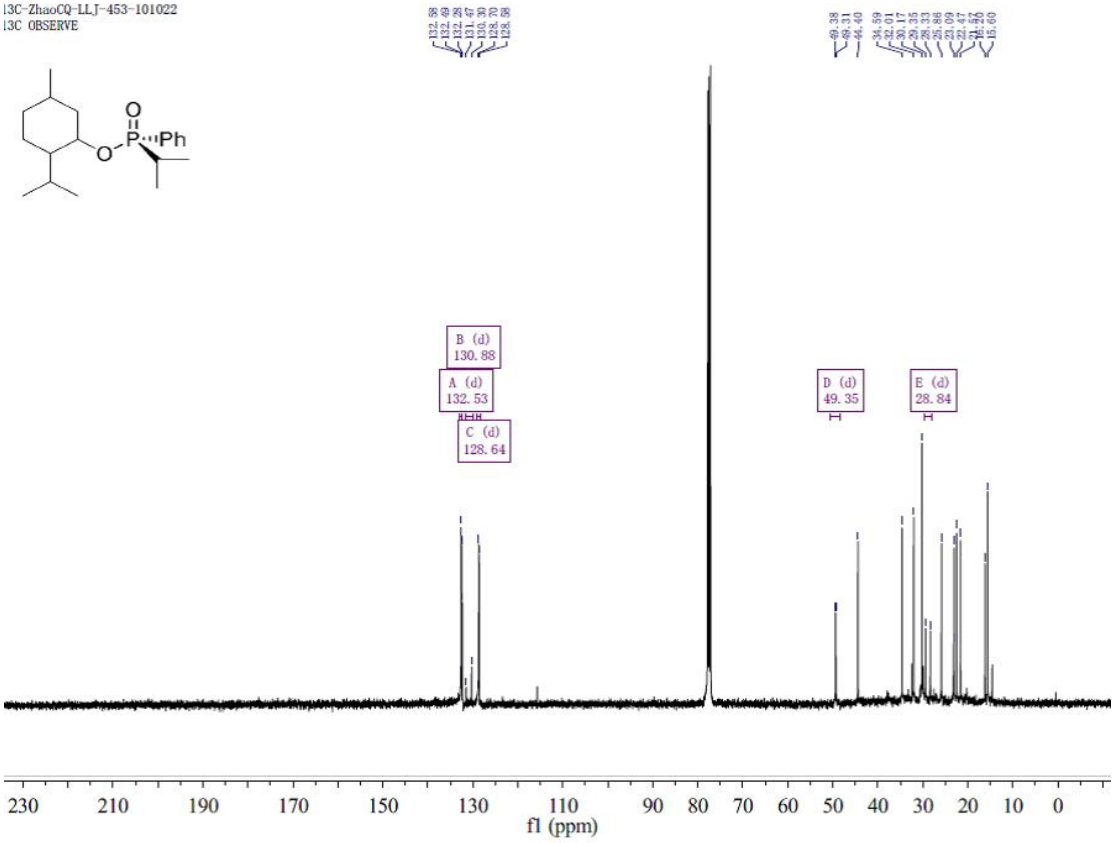
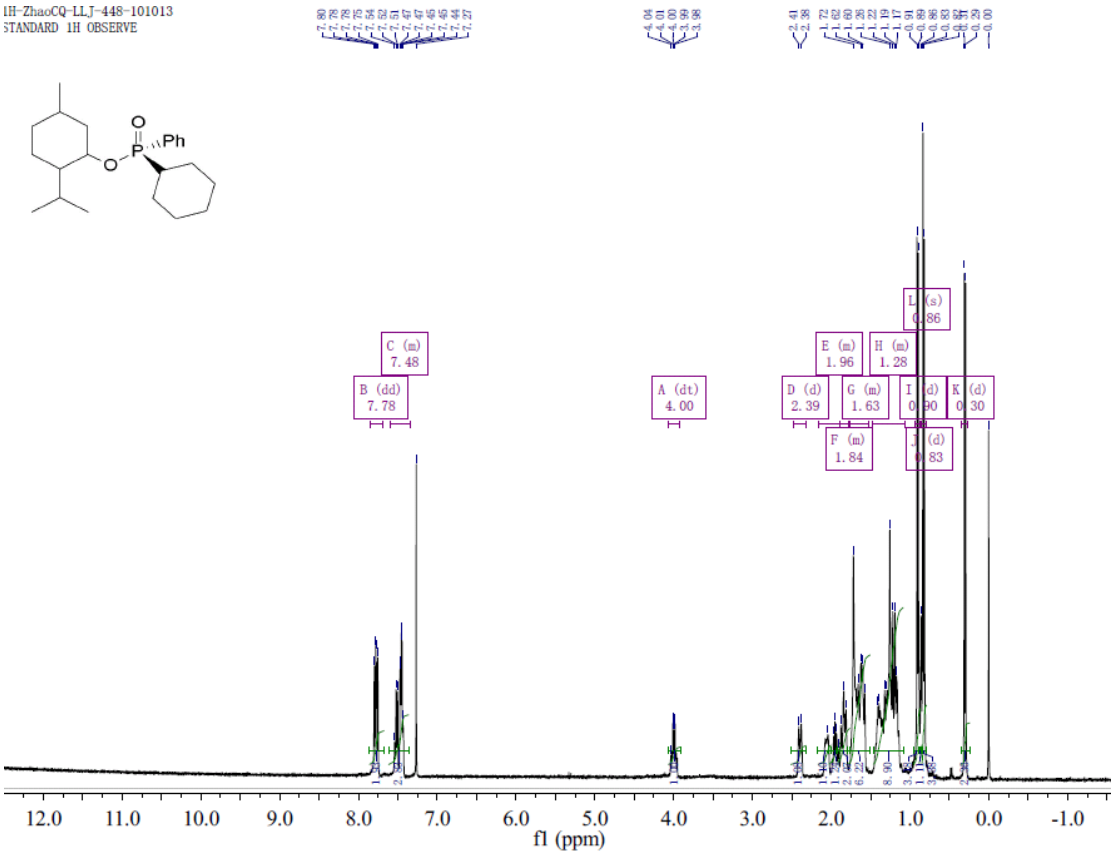


(S_P)-*O*-Menthyl *i*-propylmethylphenylphosphinate (12d)



(S_P)-*O*-Menthyl *cyclo*-hexylphenylphosphinate (12e)



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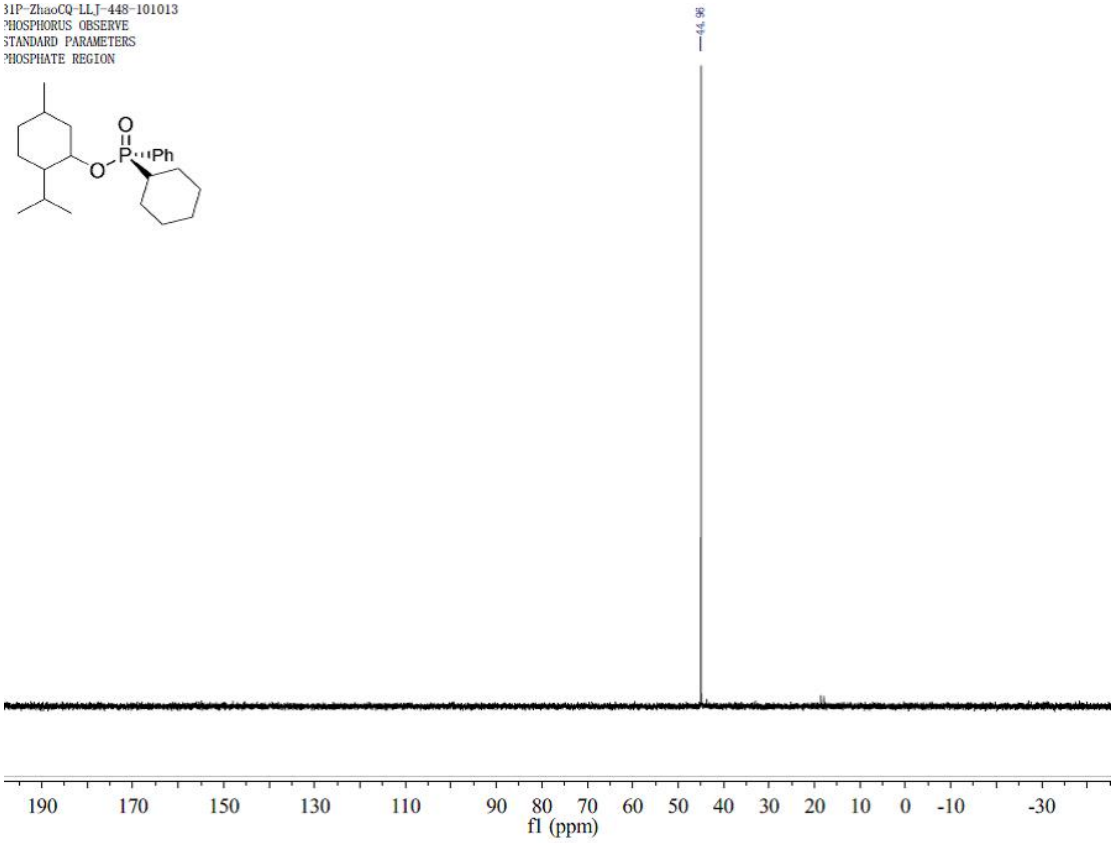
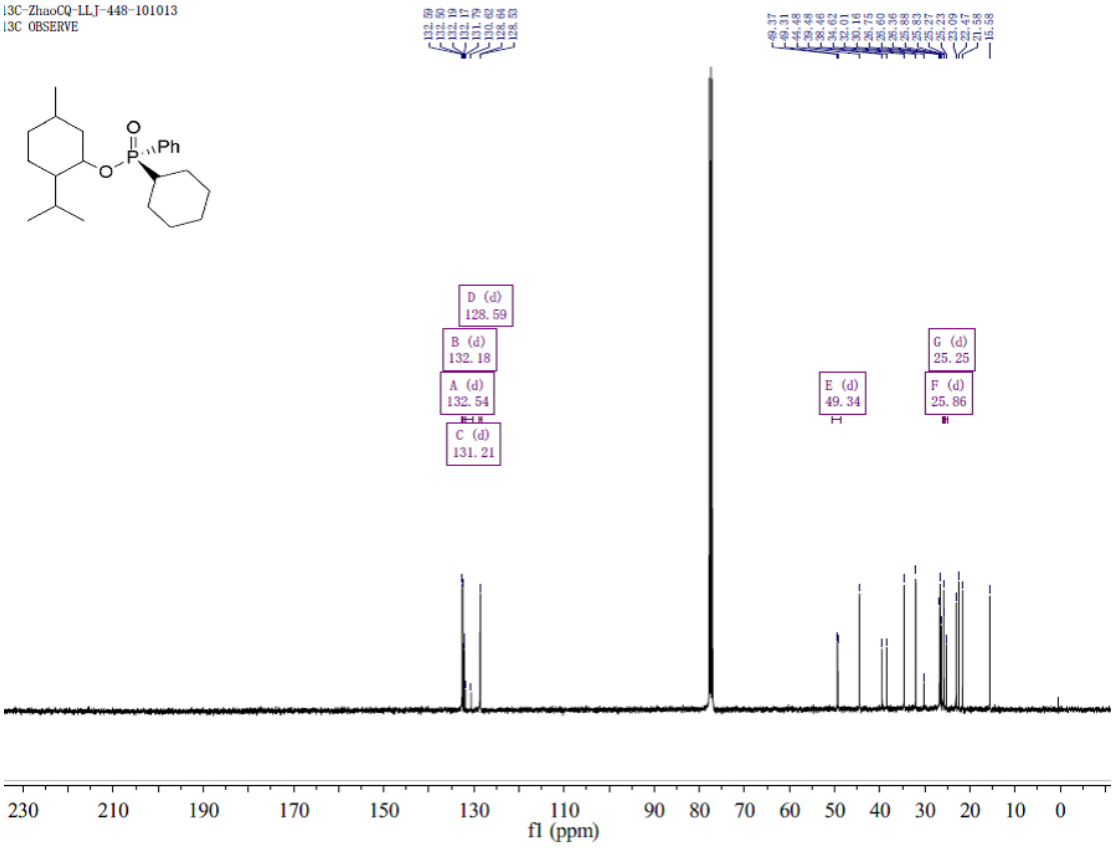
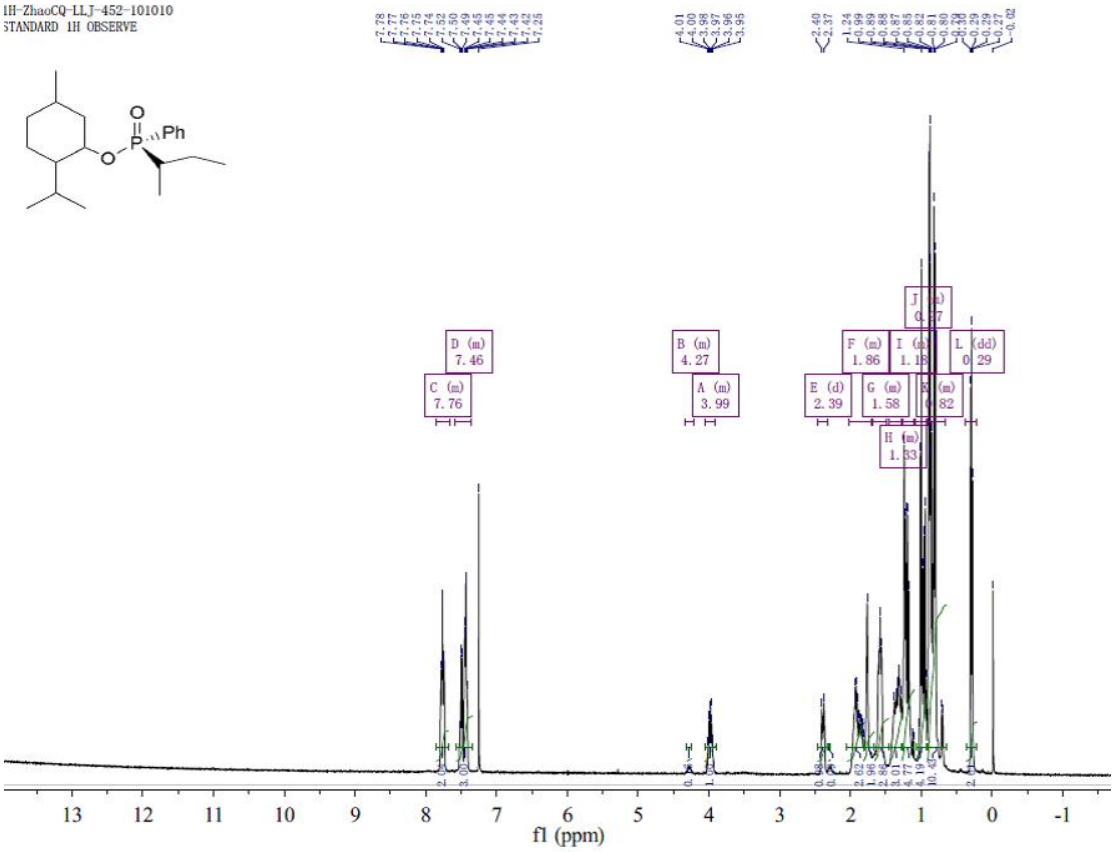


(S_P)-*O*-Menthyl *cyclo*-hexylphenylphosphinate (12e)



(S_P)-*O*-Menthyl *s*-butylphenylphosphinate (12f)



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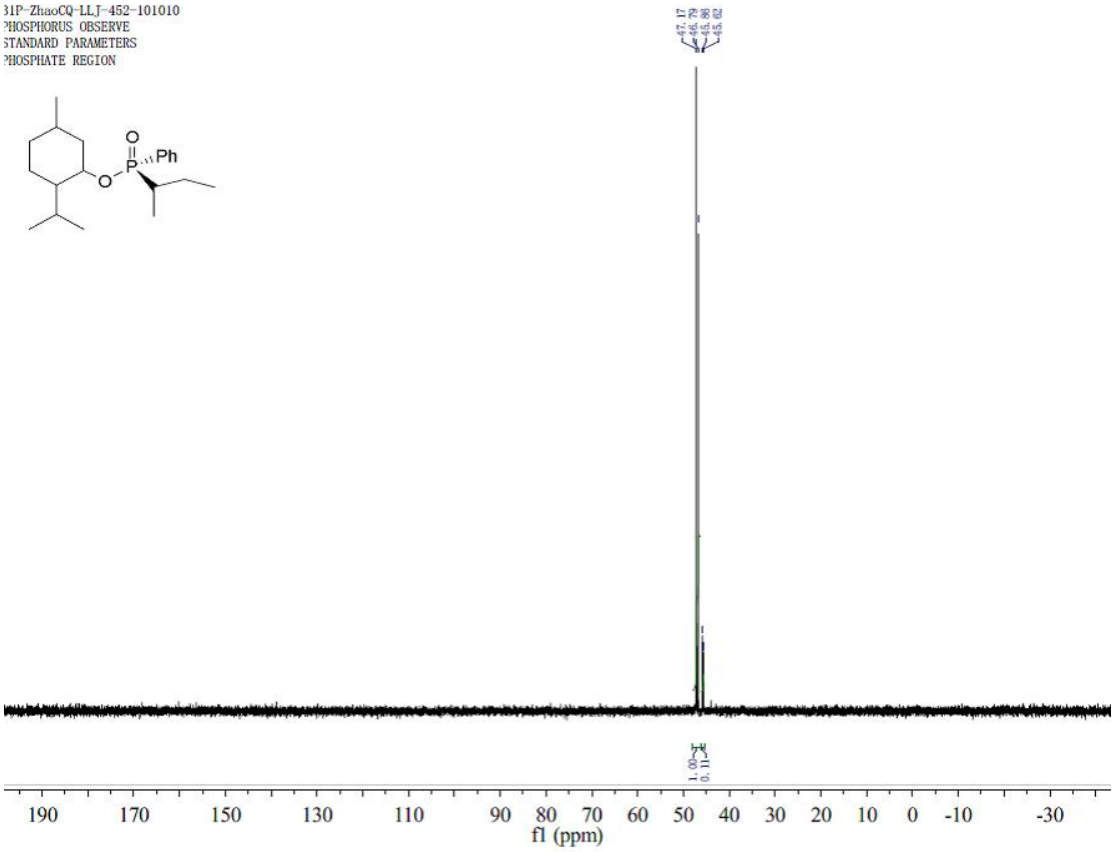

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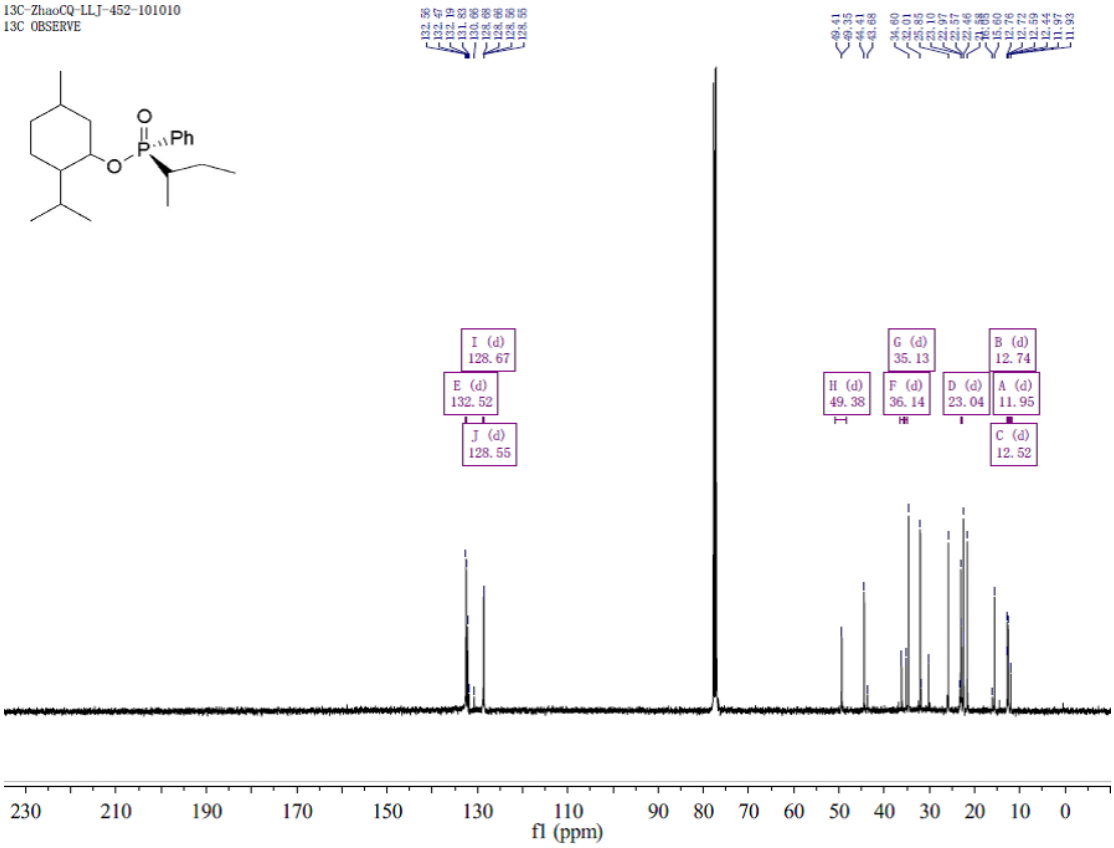

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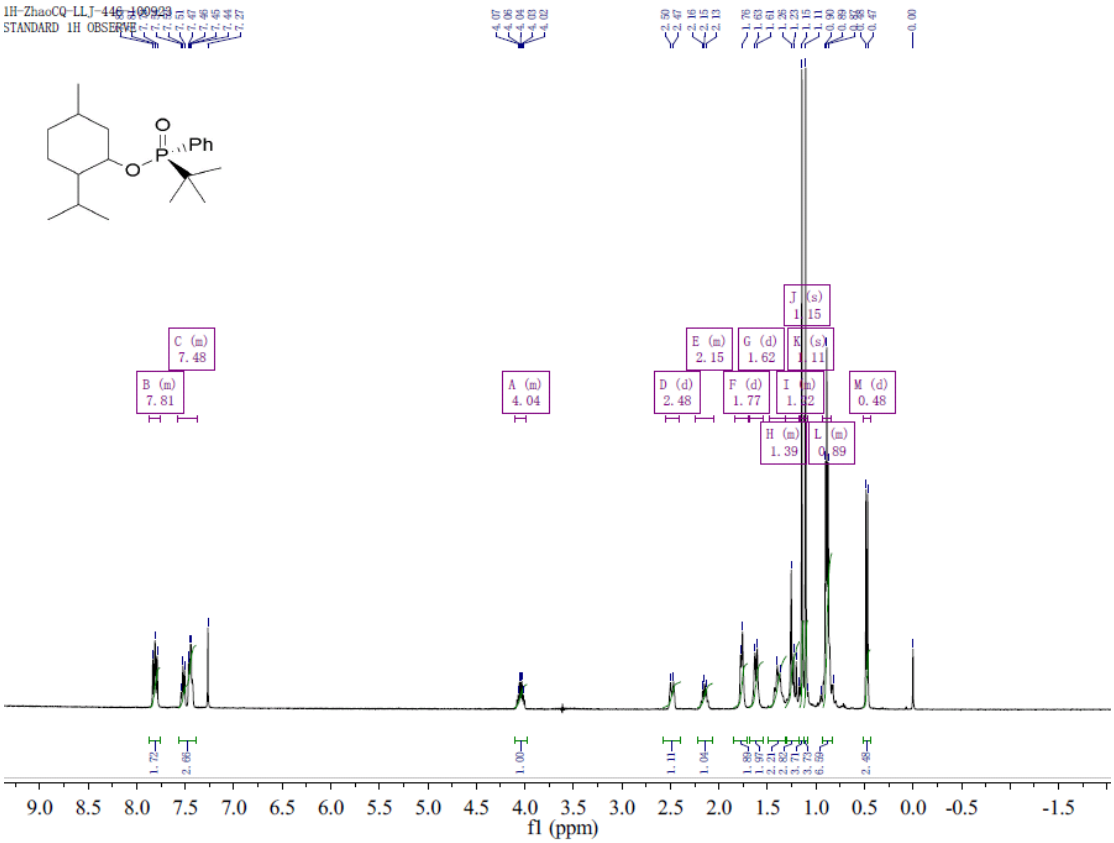
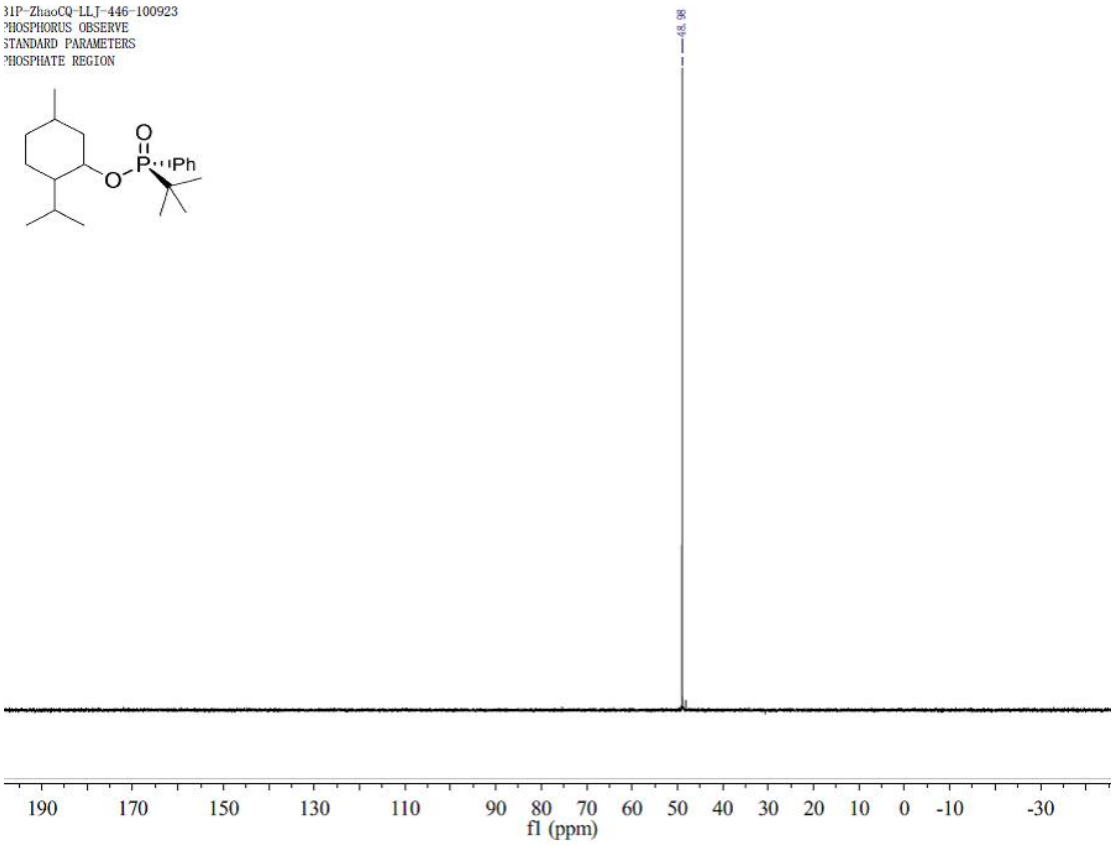
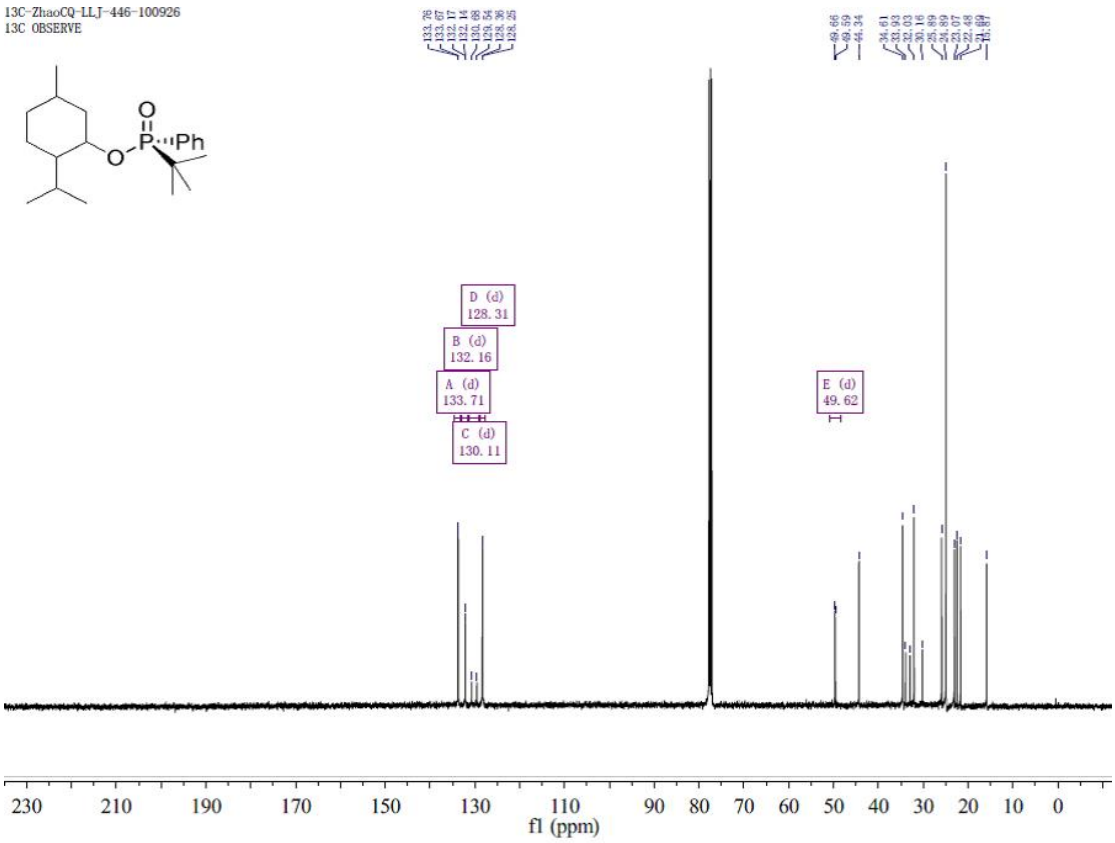


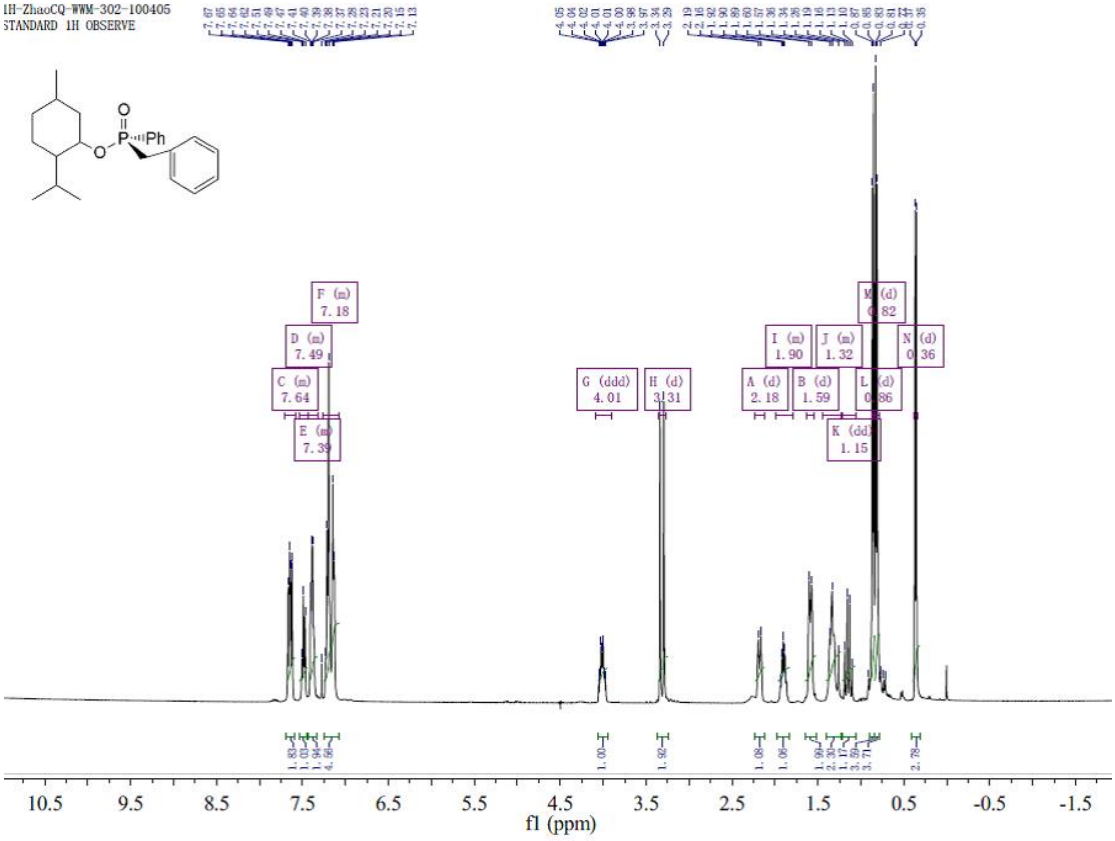
(S_P)-*O*-Menthyl *t*-butylphenylphosphinate (12g)



(S_P)-*O*-Menthyl *t*-butylphenylphosphinate (12g)



(S_P)-*O*-Menthyl benzylphenylphosphinate (12h)



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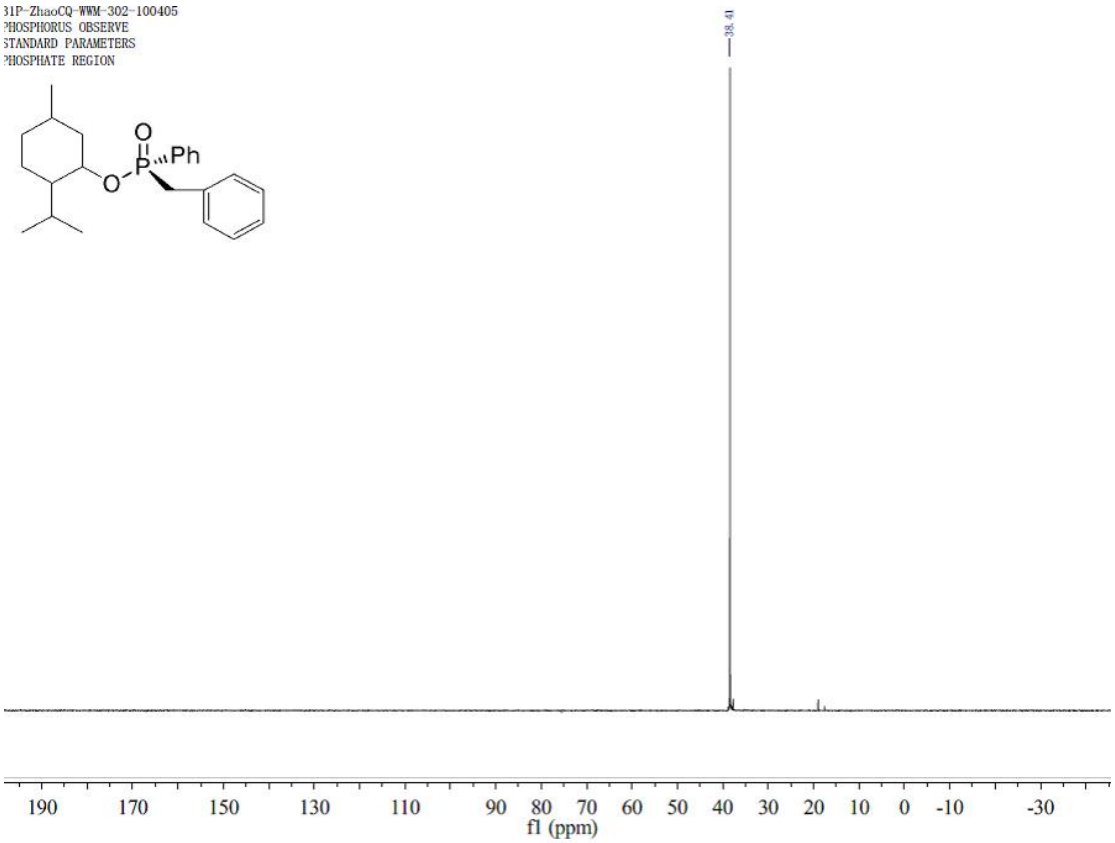
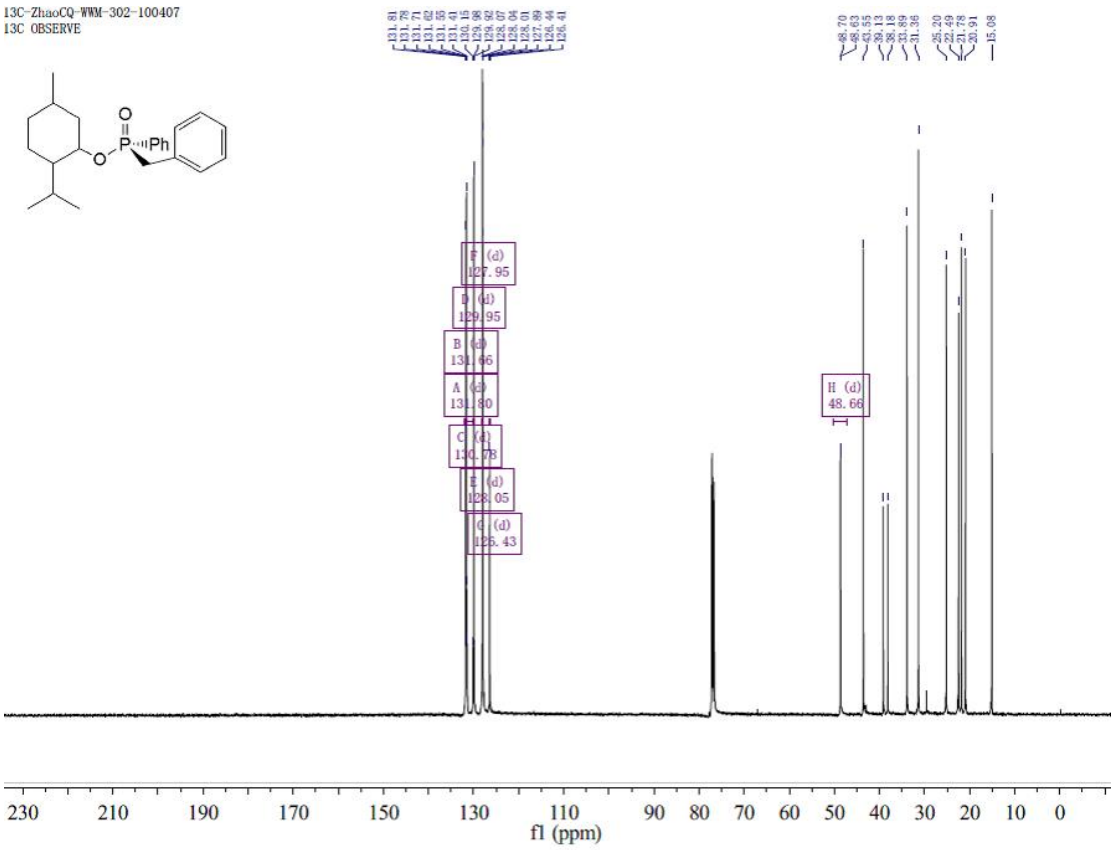
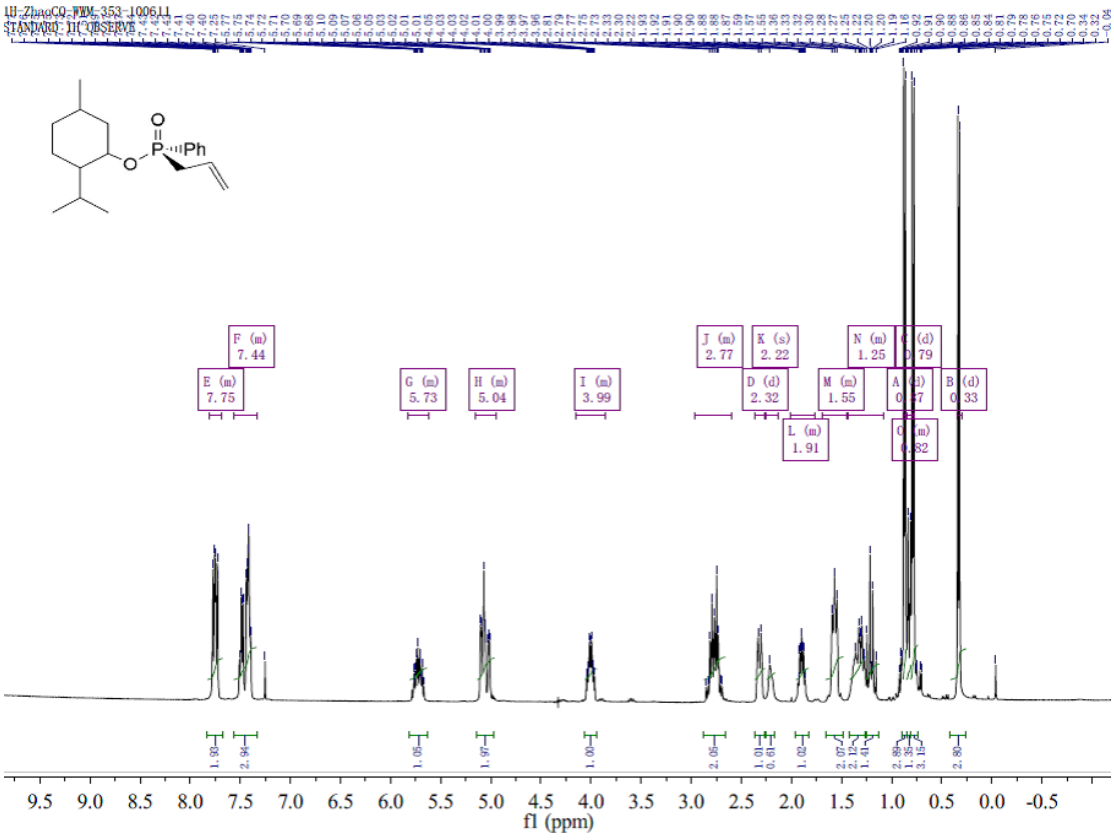


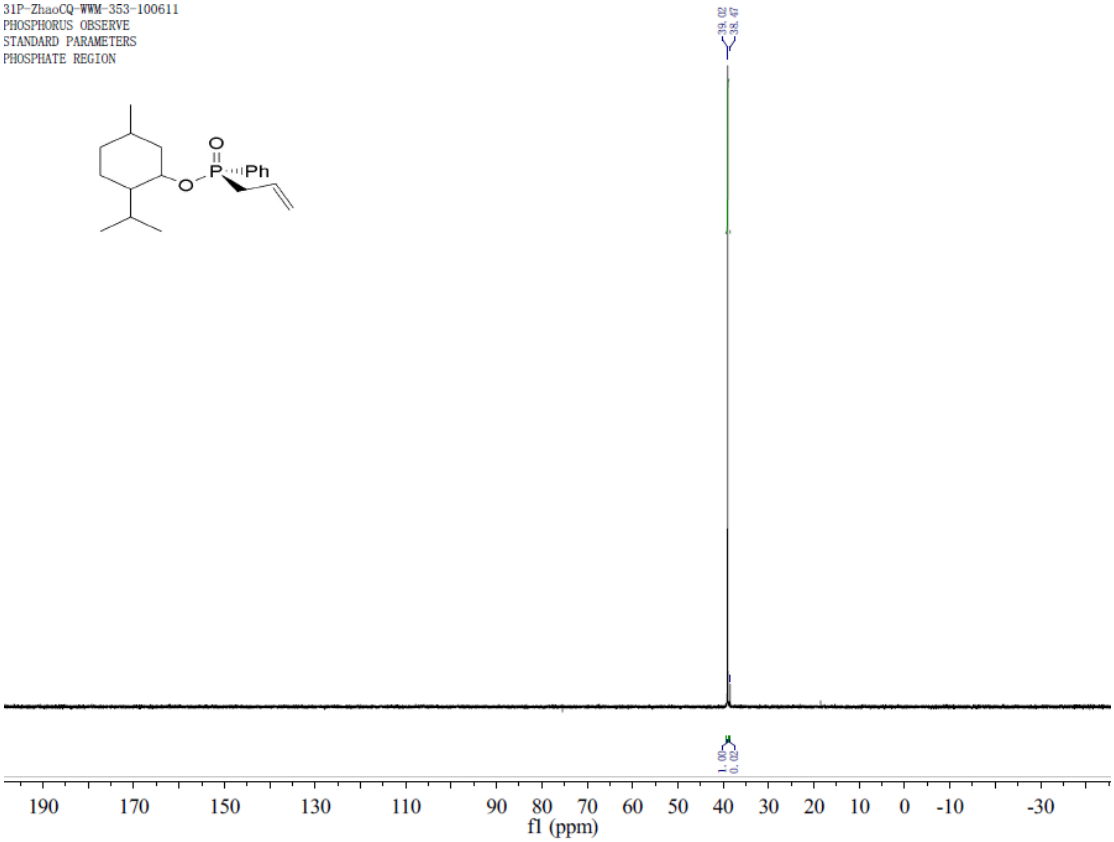
(S_P)-*O*-Menthyl benzylphenylphosphinate (12h)



(S_P)-*O*-Menthyl allylphenylphosphinate (12i)



(S_P)-*O*-Menthyl allylphenylphosphinate (12i)



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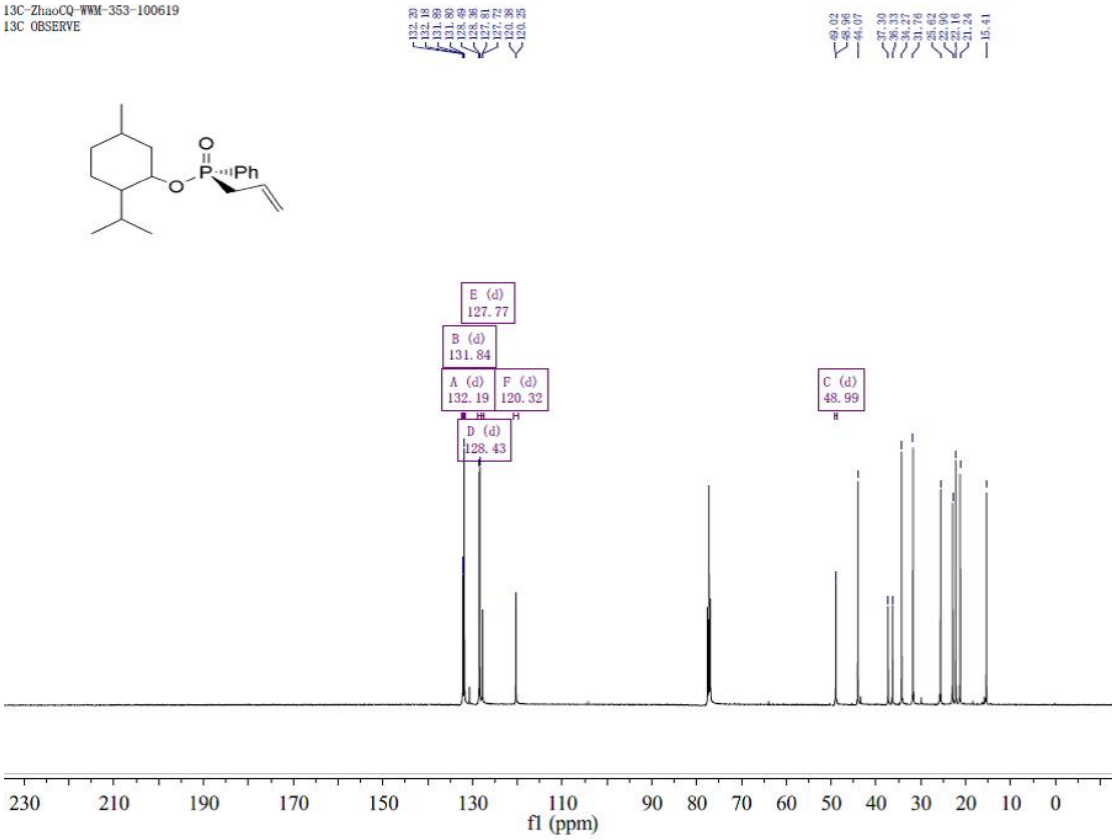
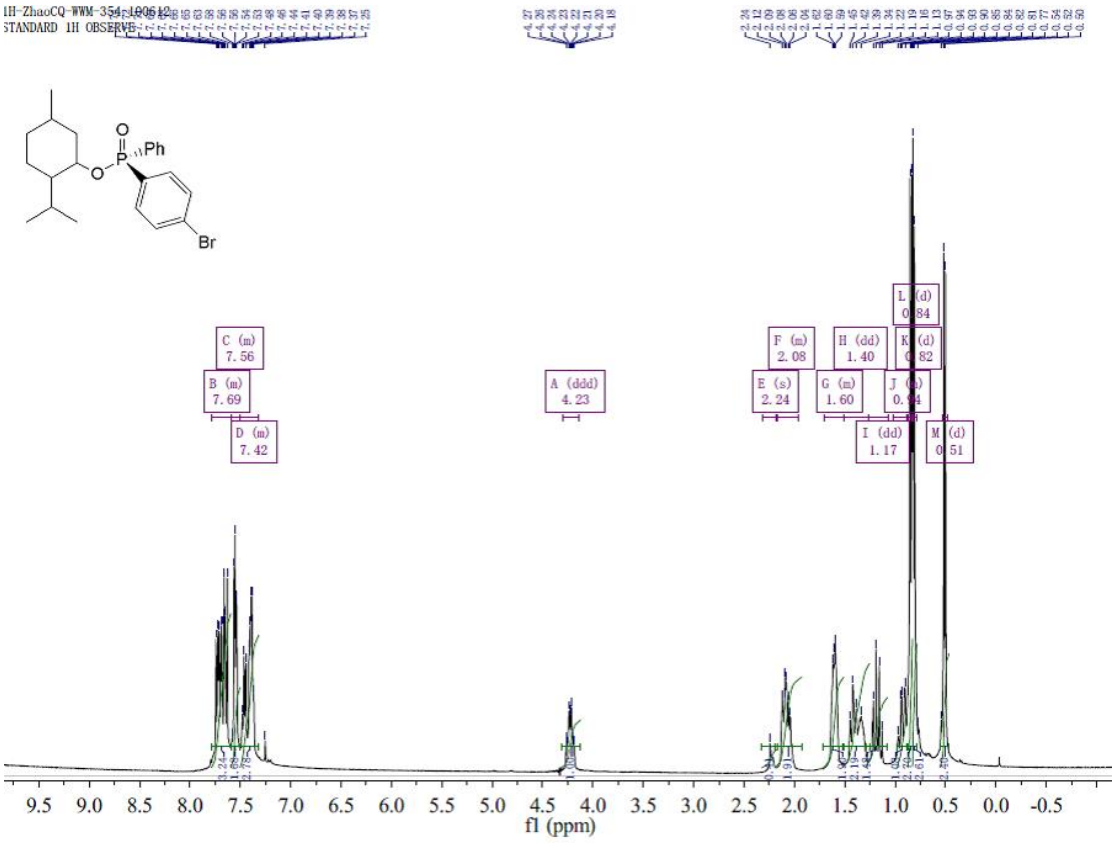
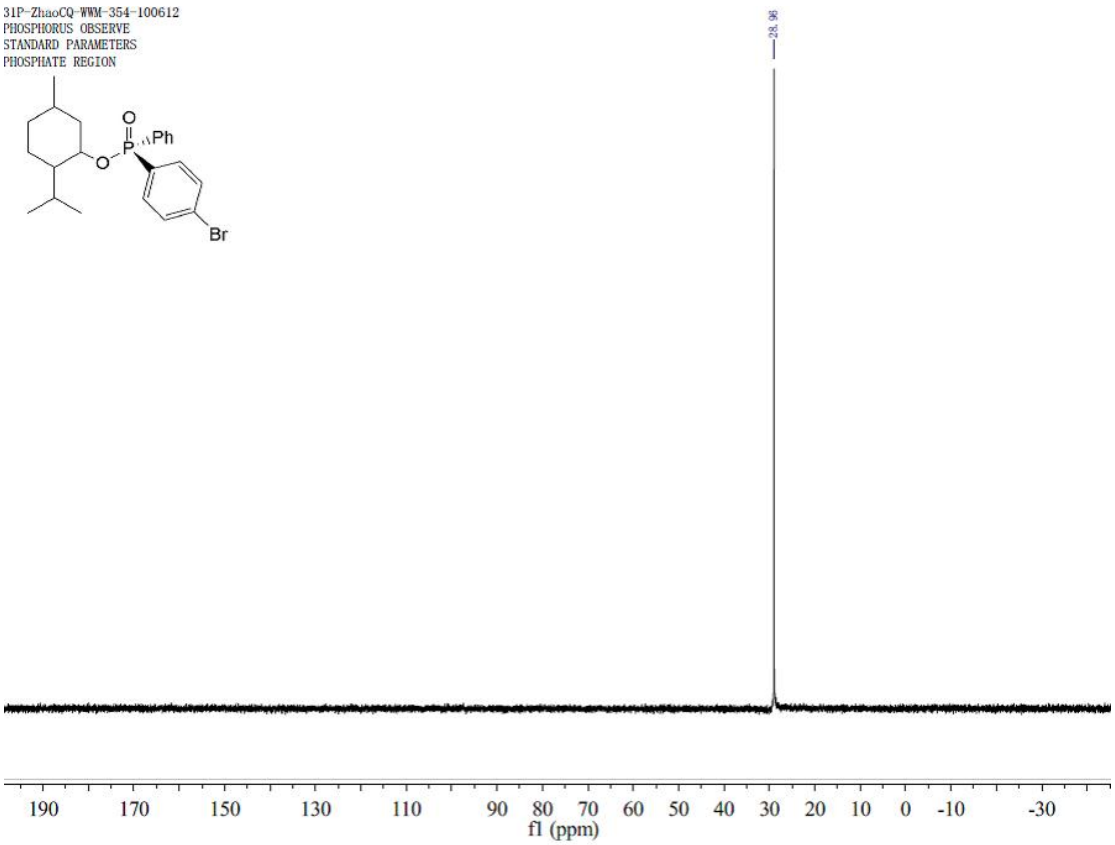


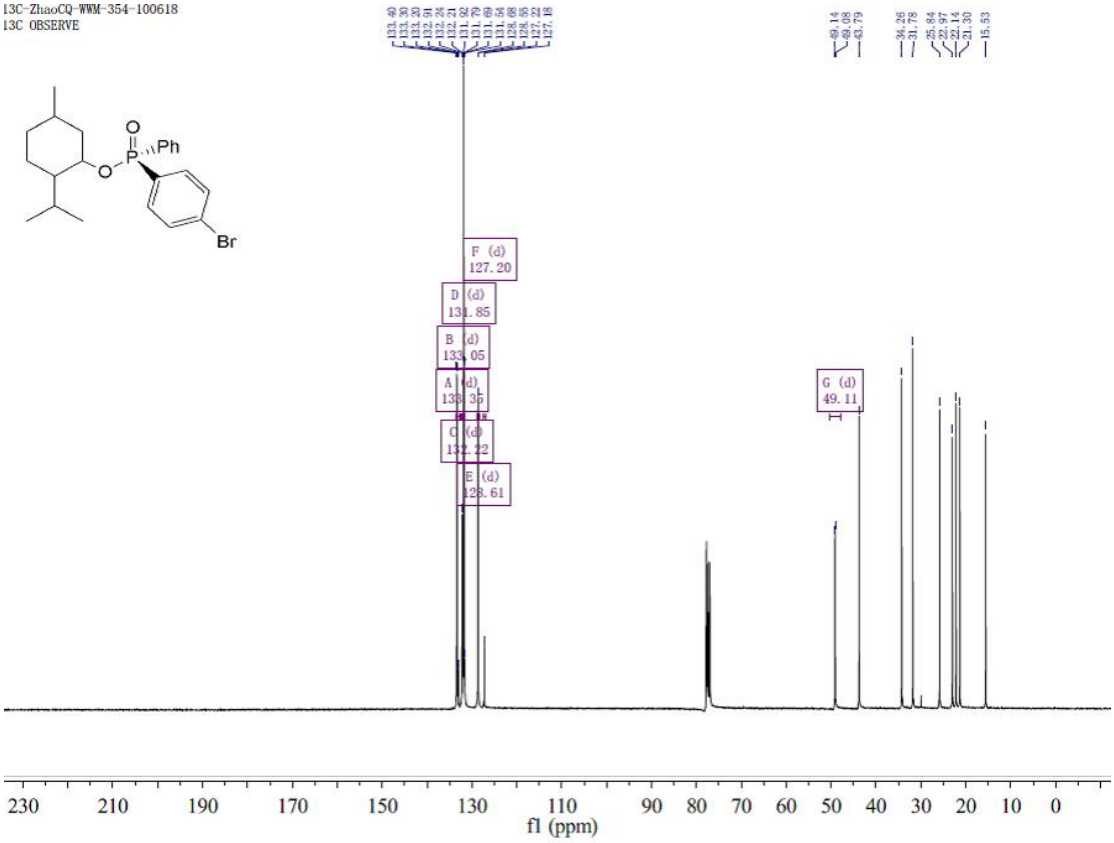
(R_P)-*O*-Menthyl *p*-bromophenylphenylphosphinate (12j)



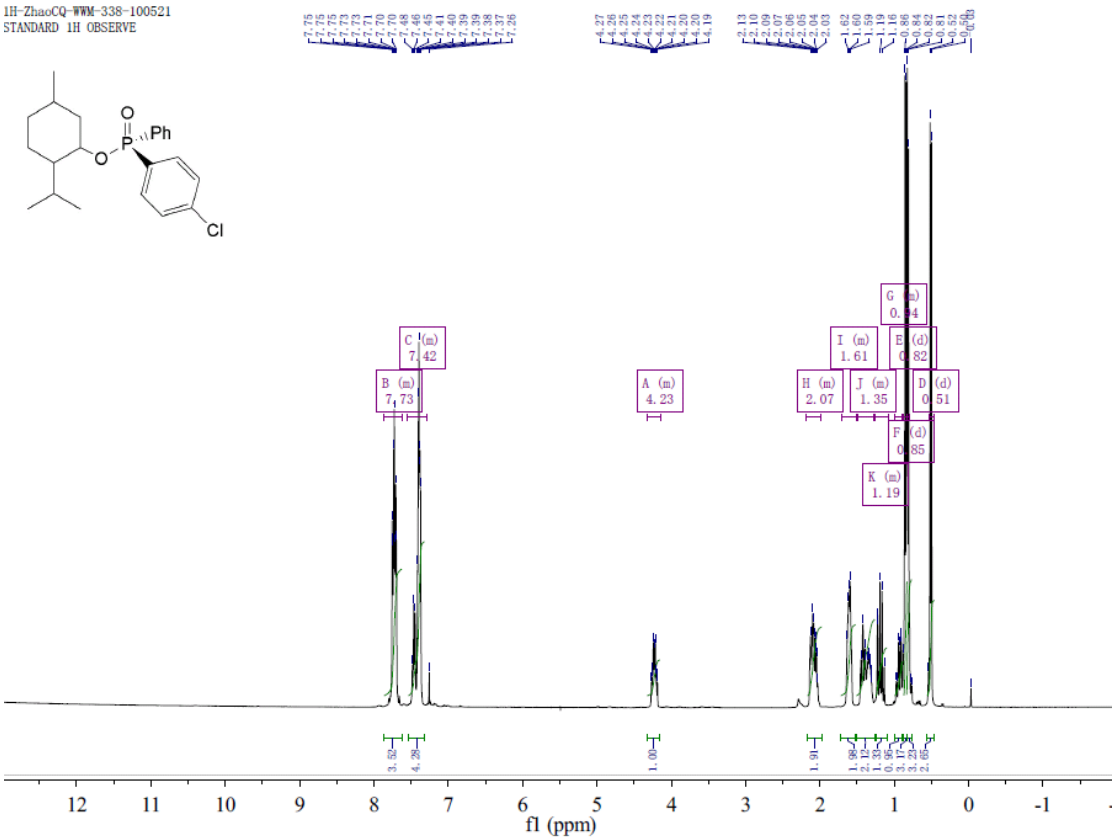
(R_P)-*O*-Menthyl *p*-bromophenylphenylphosphinate (12j)



(R_P)-*O*-Menthyl *p*-bromophenylphenylphosphinate (12j)



(R_P)-*O*-Menthyl *p*-chlorophenylphenylphosphinate (12k)



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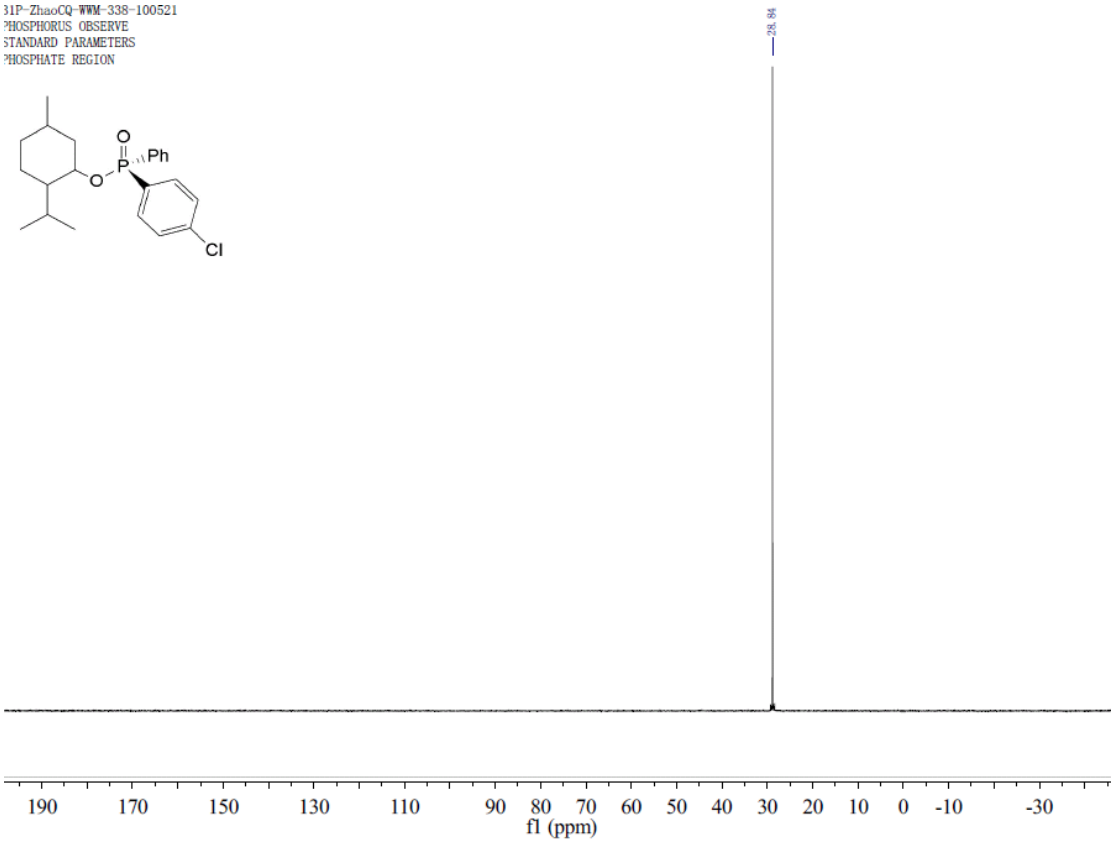
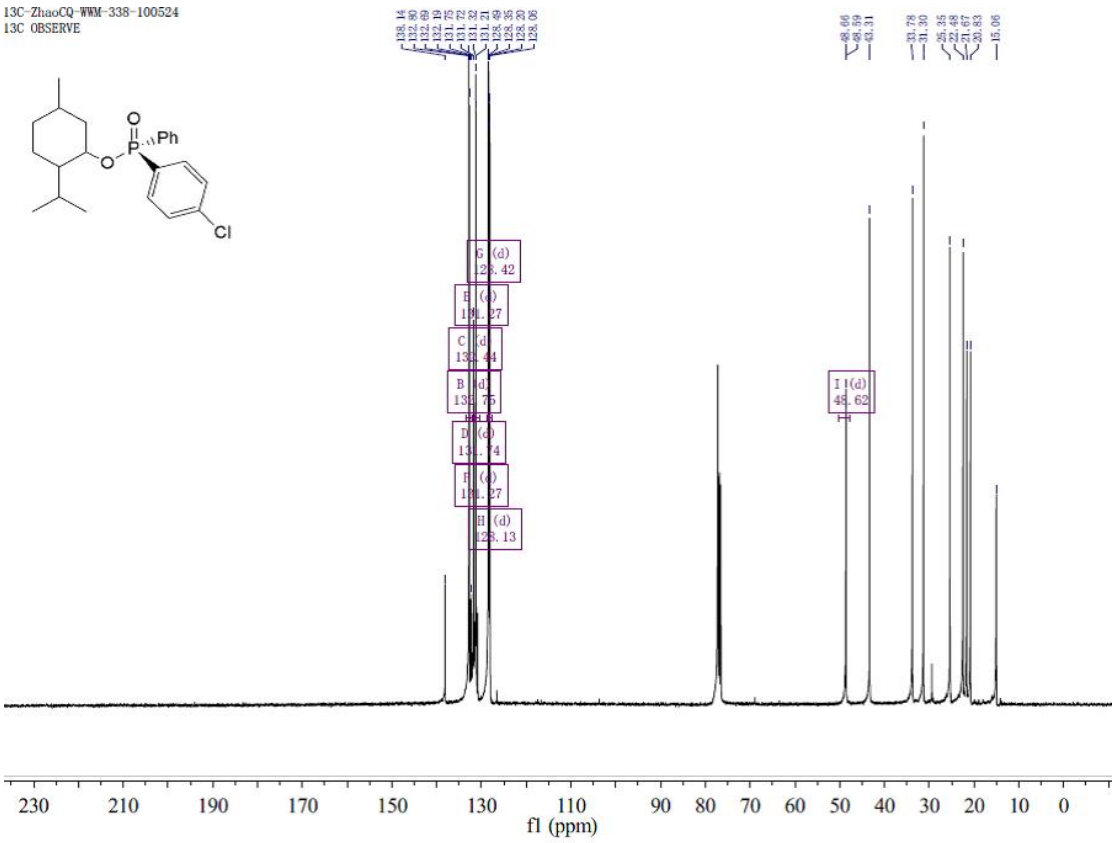
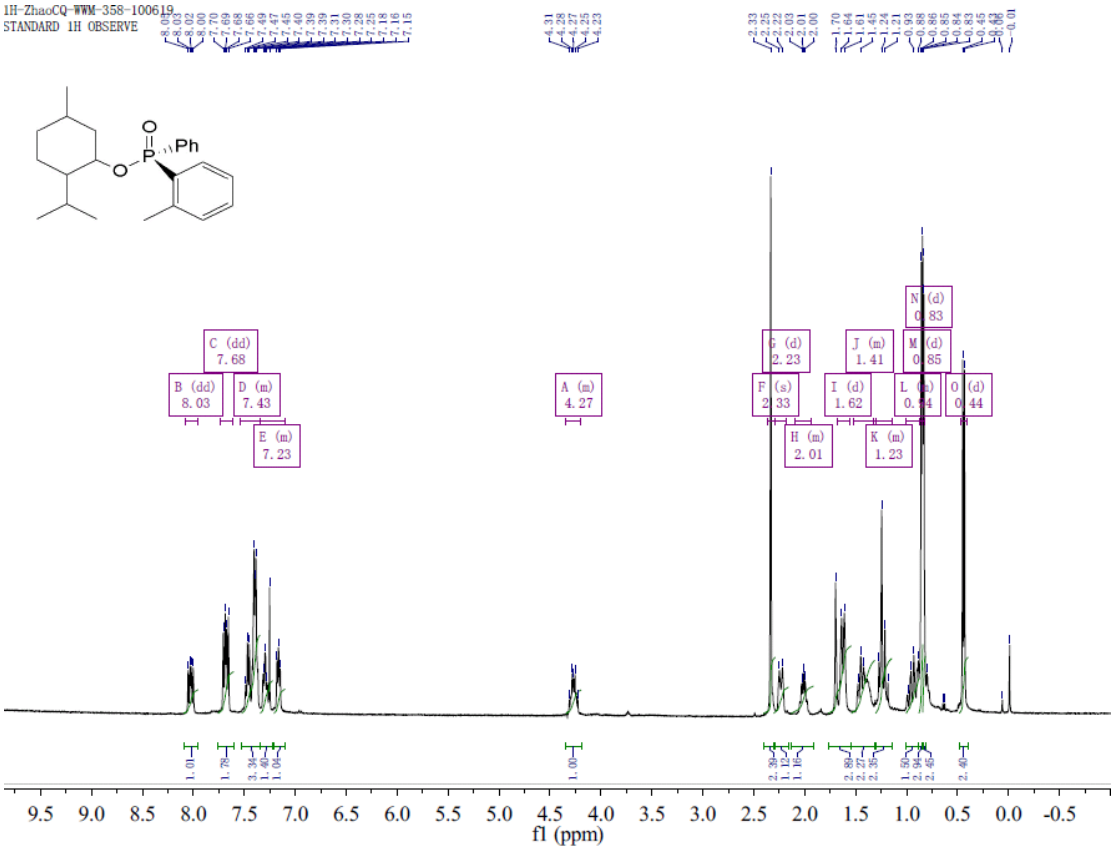


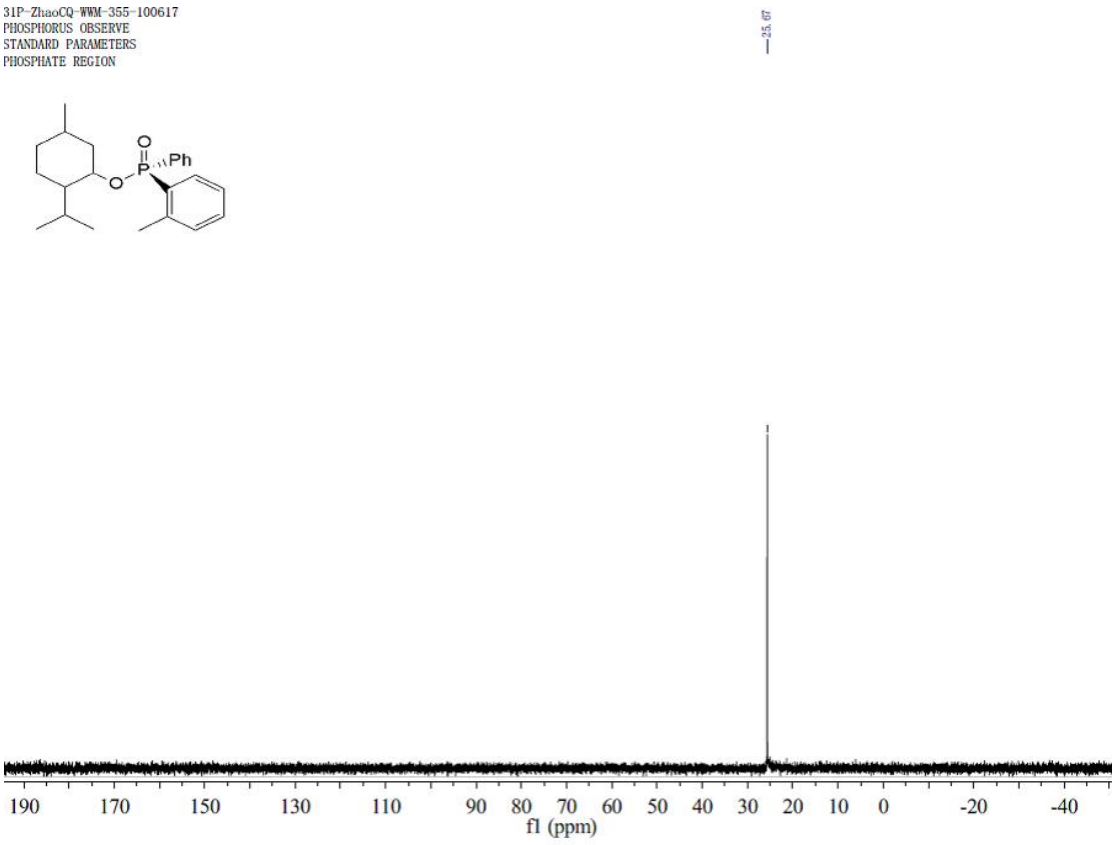
(R_P)-*O*-Menthyl *p*-chlorophenylphenylphosphinate (12k)



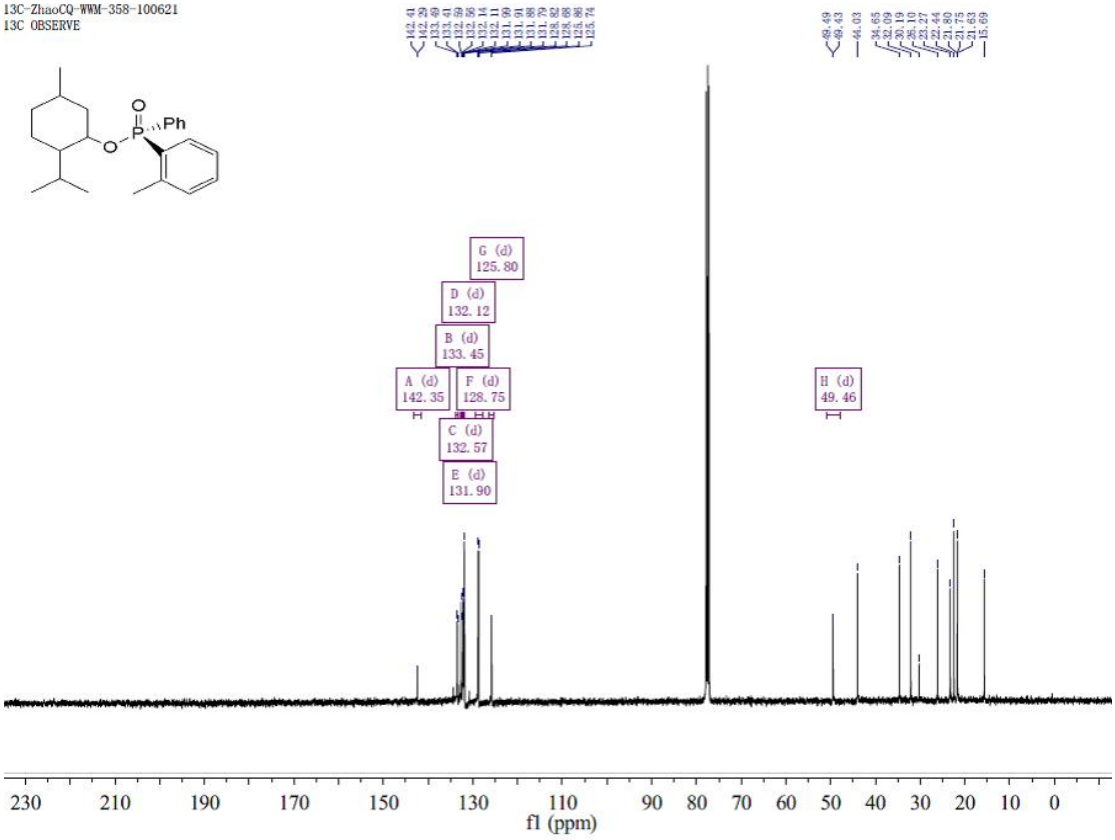
(R_P)-*O*-Menthyl *o*-methylphenylphenylphosphinate (12l)



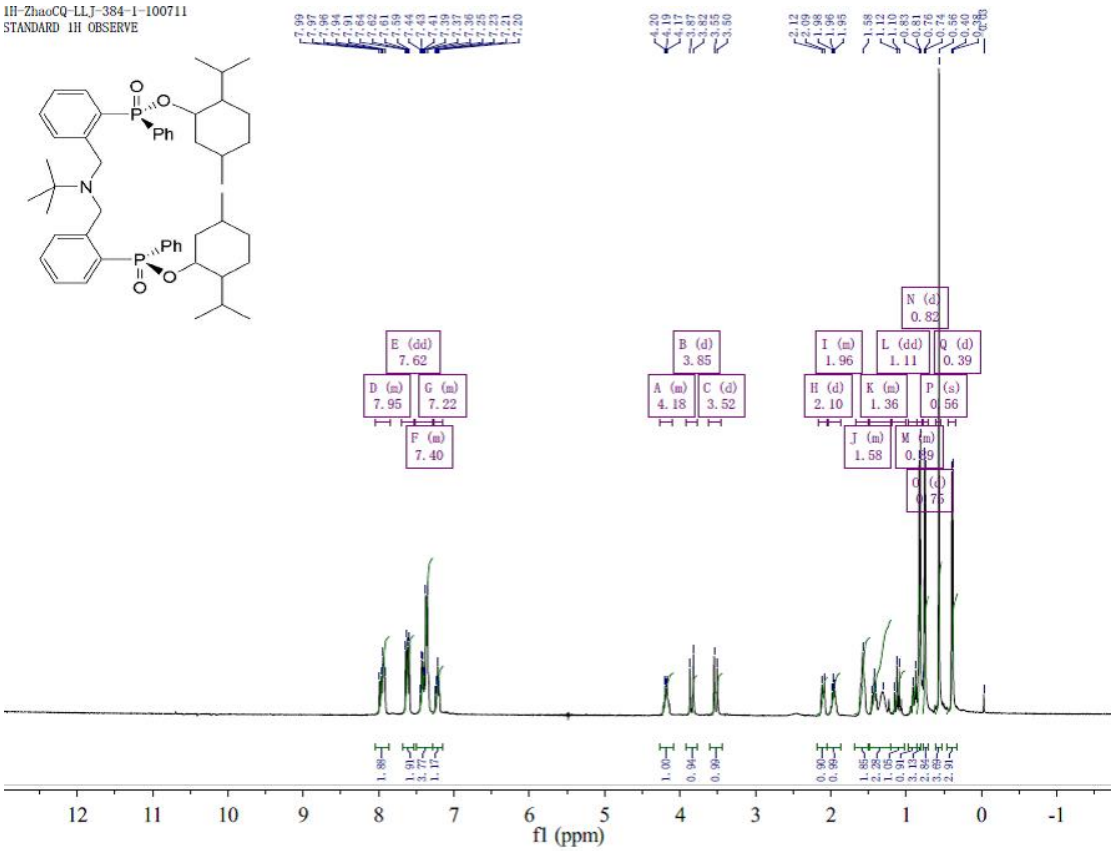
(R_P)-*O*-Menthyl *o*-methylphenylphenylphosphinate (12l)



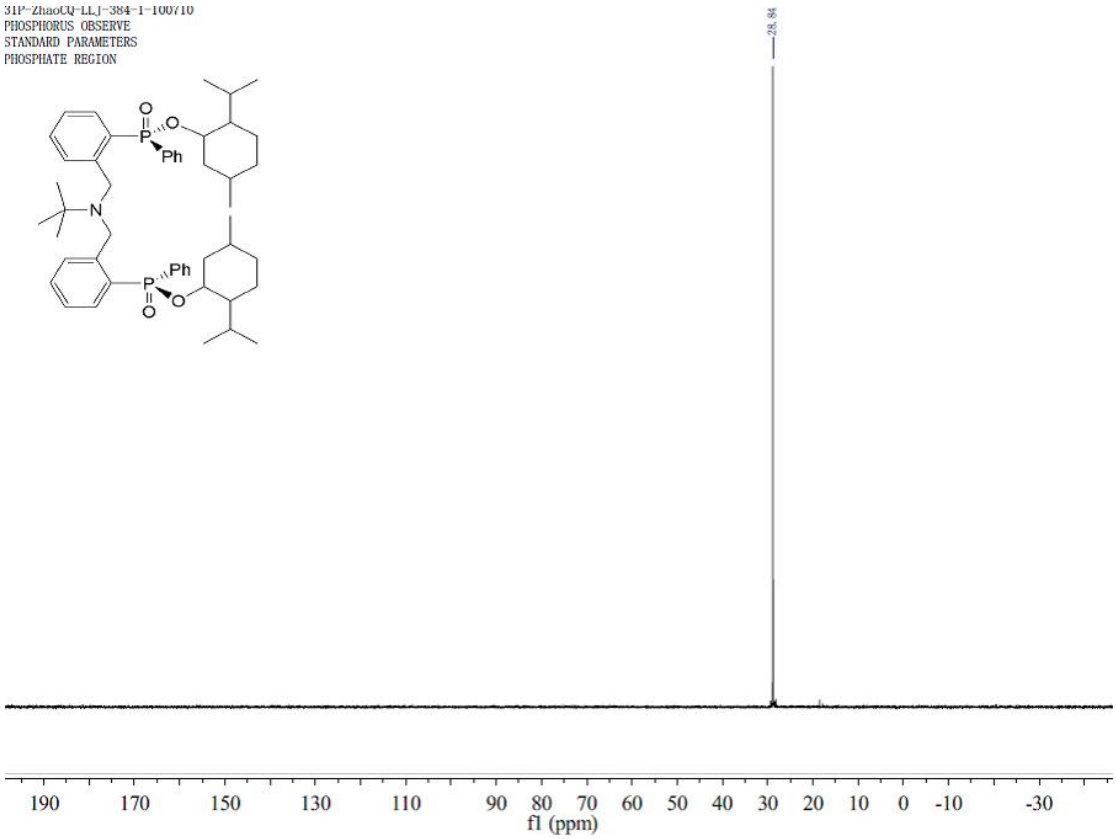
(R_P)-*O*-Menthyl *o*-methylphenylphenylphosphinate (12l)



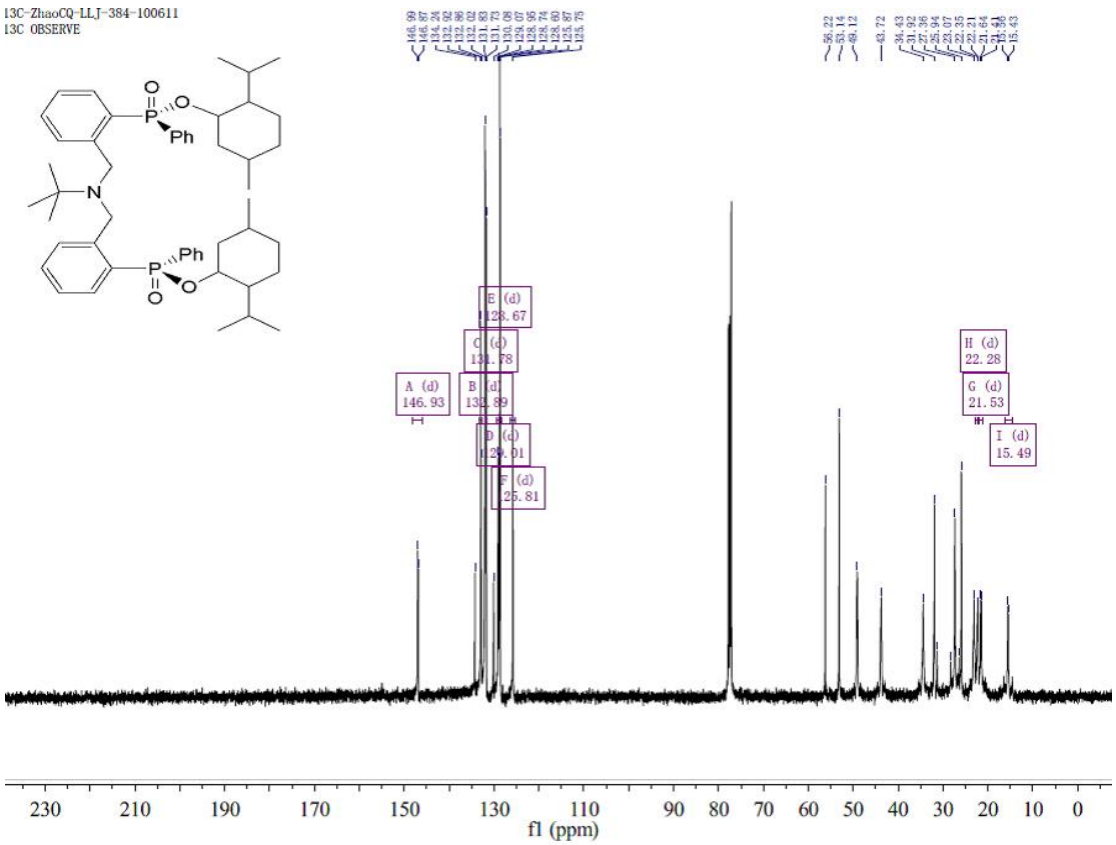
Bis-phenylphosphinate 12m



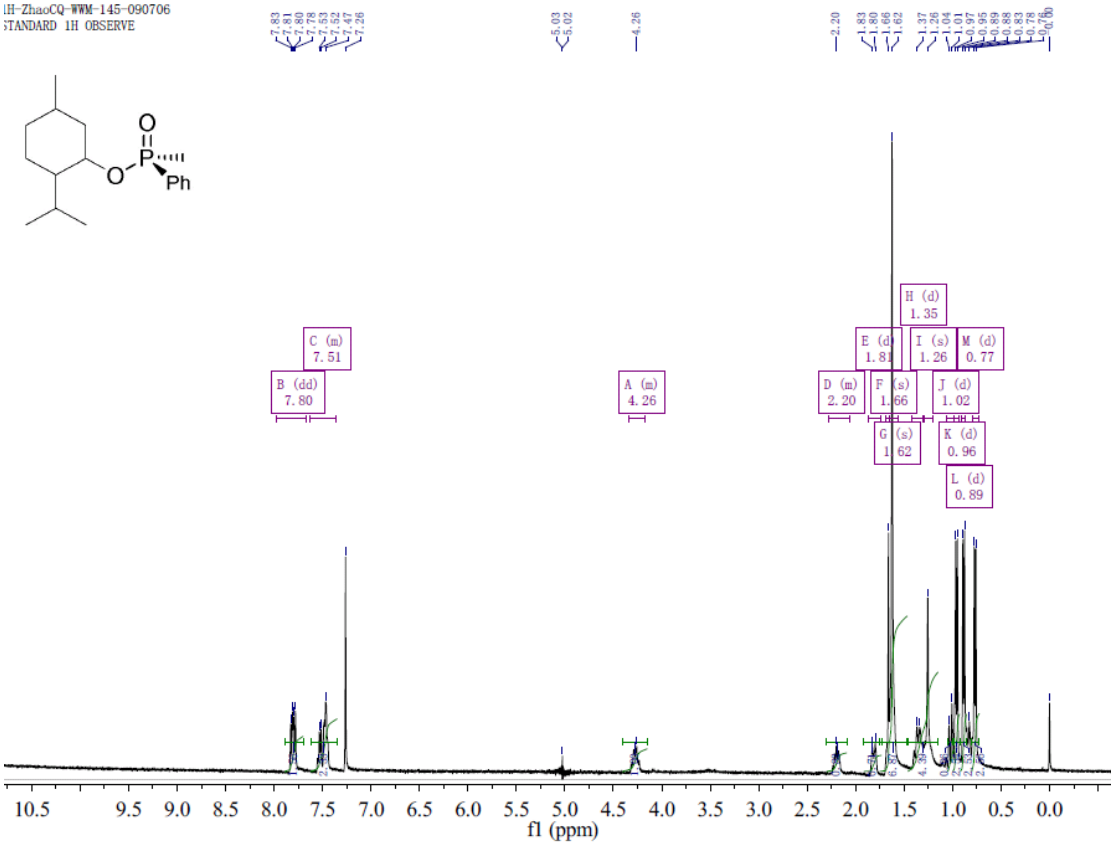
Bis-phenylphosphinate 12m



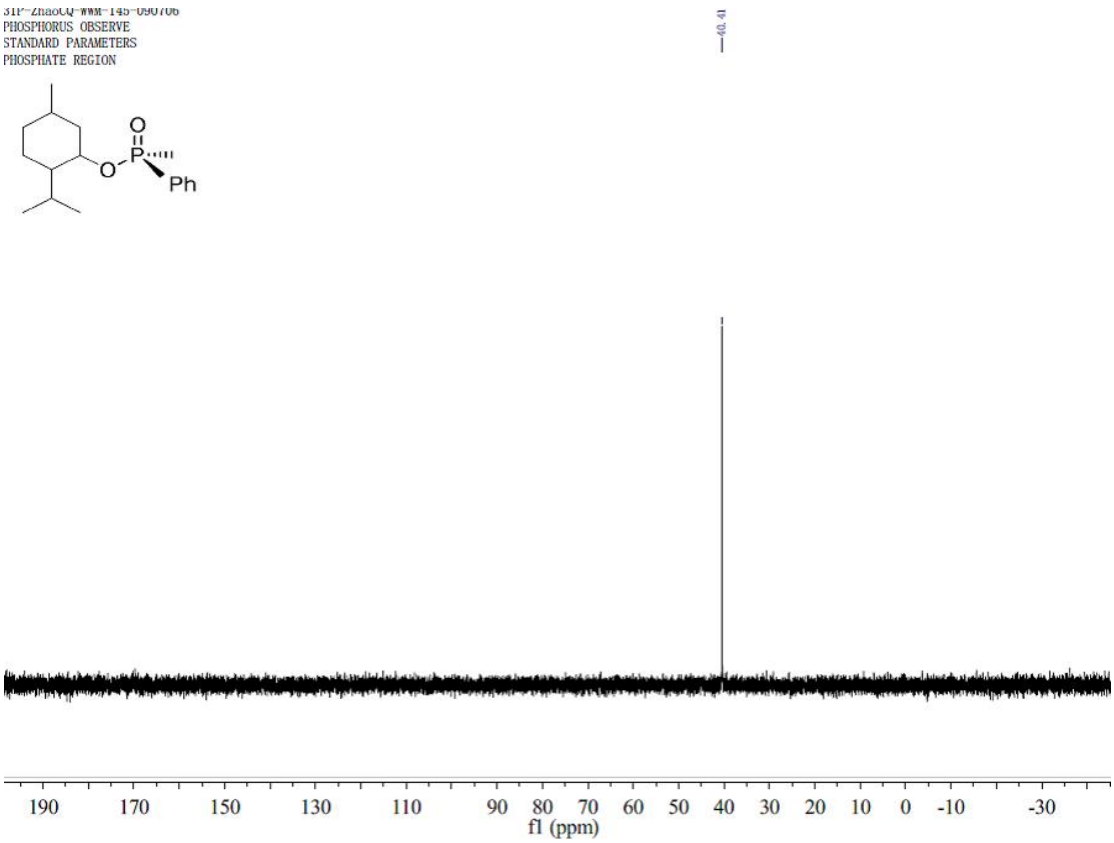
Bis-phenylphosphinate 12m



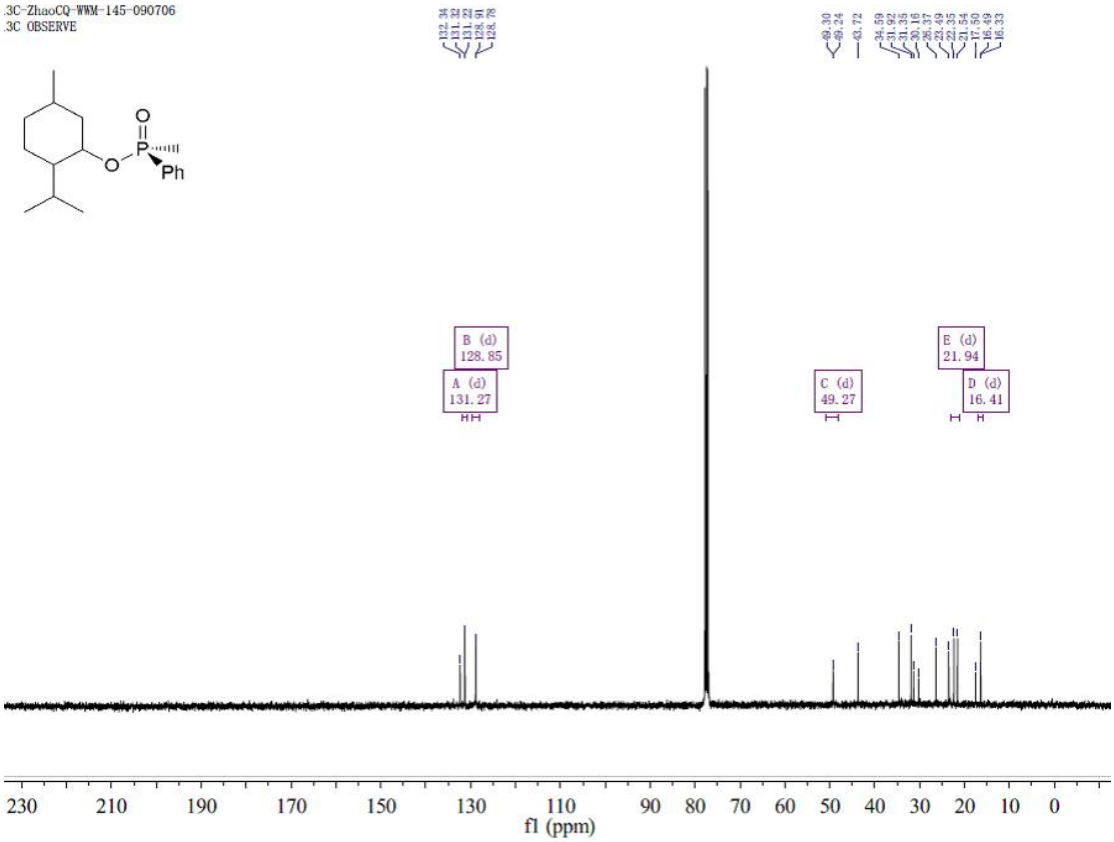
(R_P)-*O*-Menthyl methylphenylphosphinate (12a')



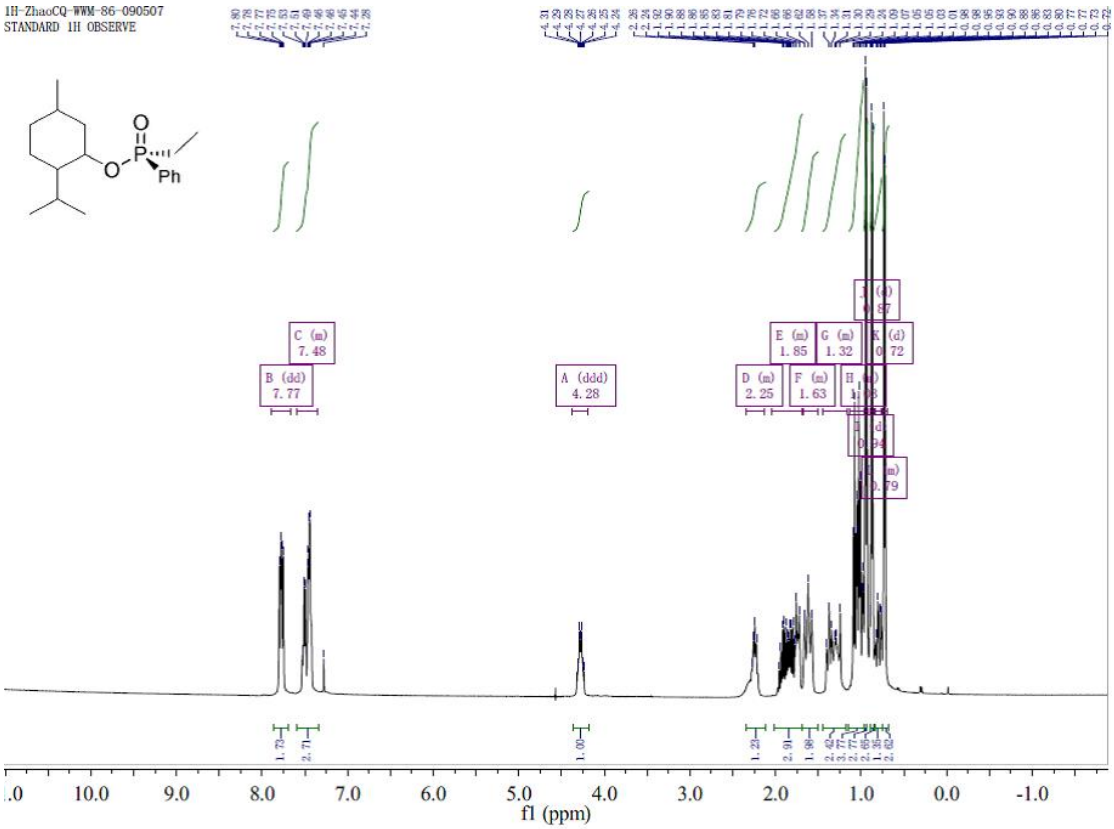
(R_P)-*O*-Menthyl methylphenylphosphinate (12a')



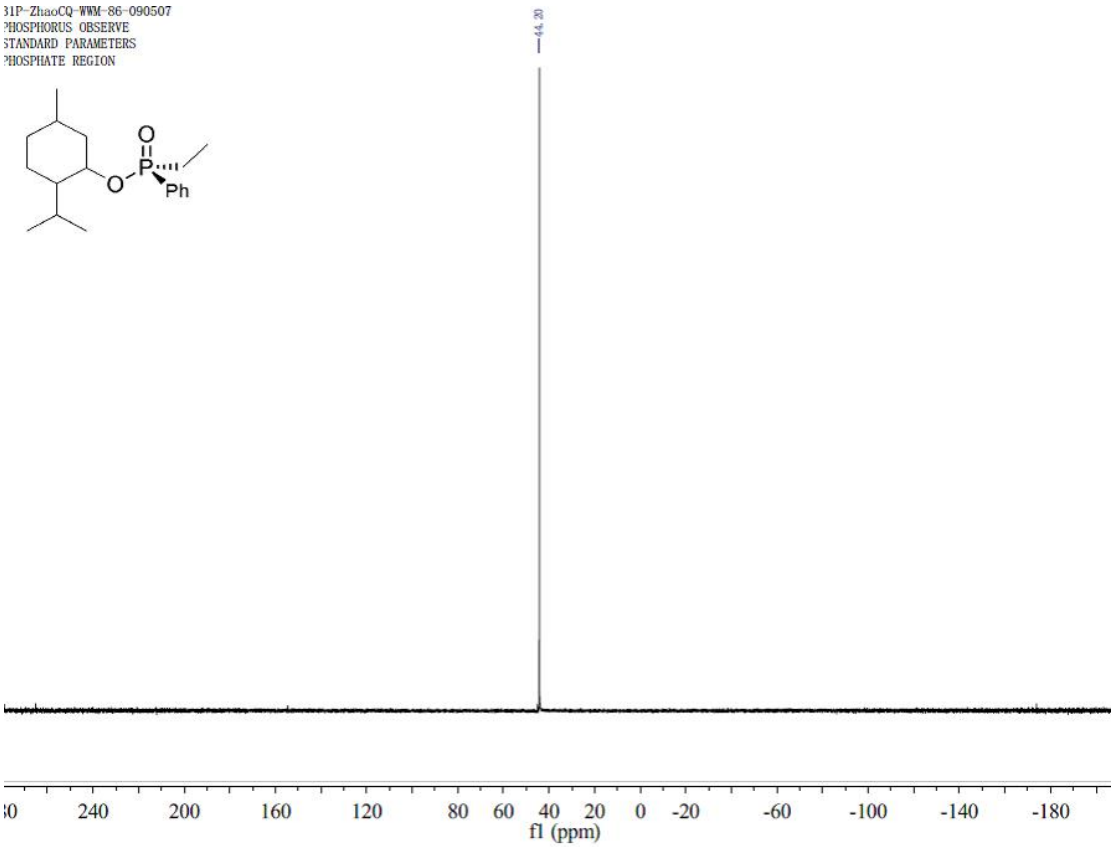
(R_P)-*O*-Menthyl methylphenylphosphinate (12a')



(R_P)-*O*-Menthyl ethylphenylphosphinate (12b')



(R_P)-*O*-Menthyl ethylphenylphosphinate (12b')



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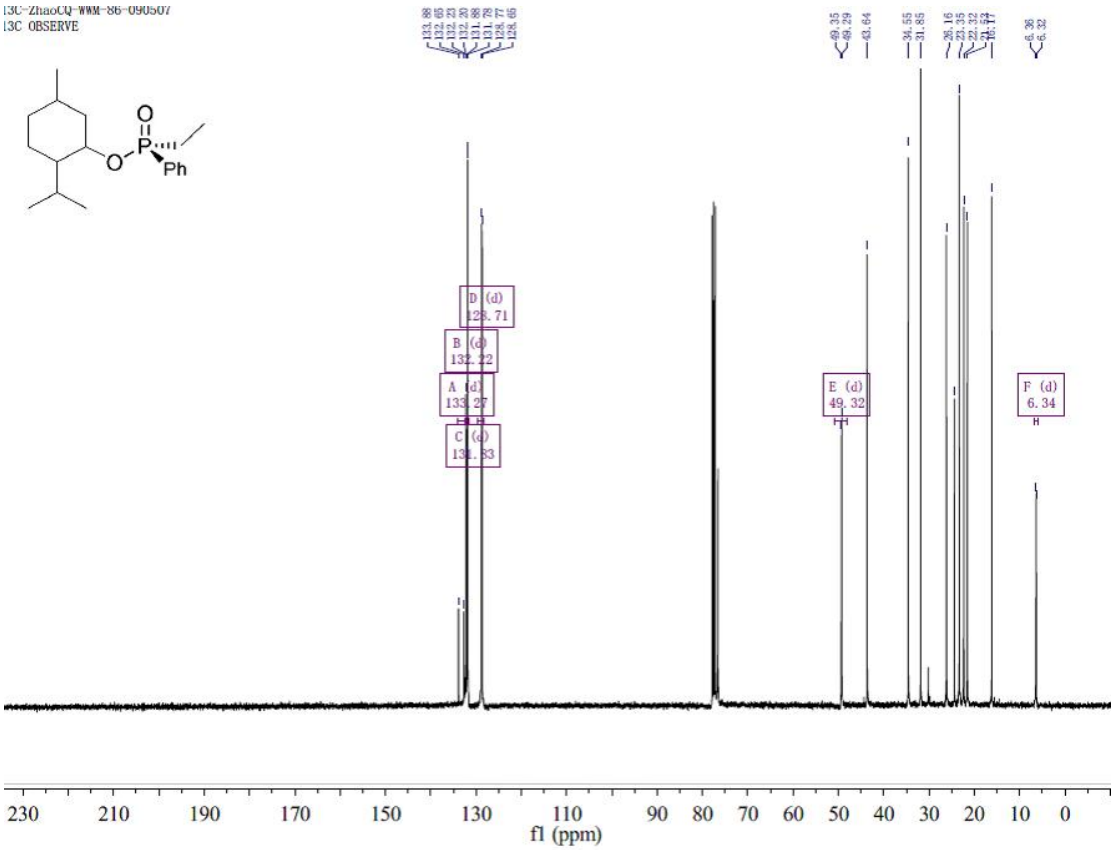
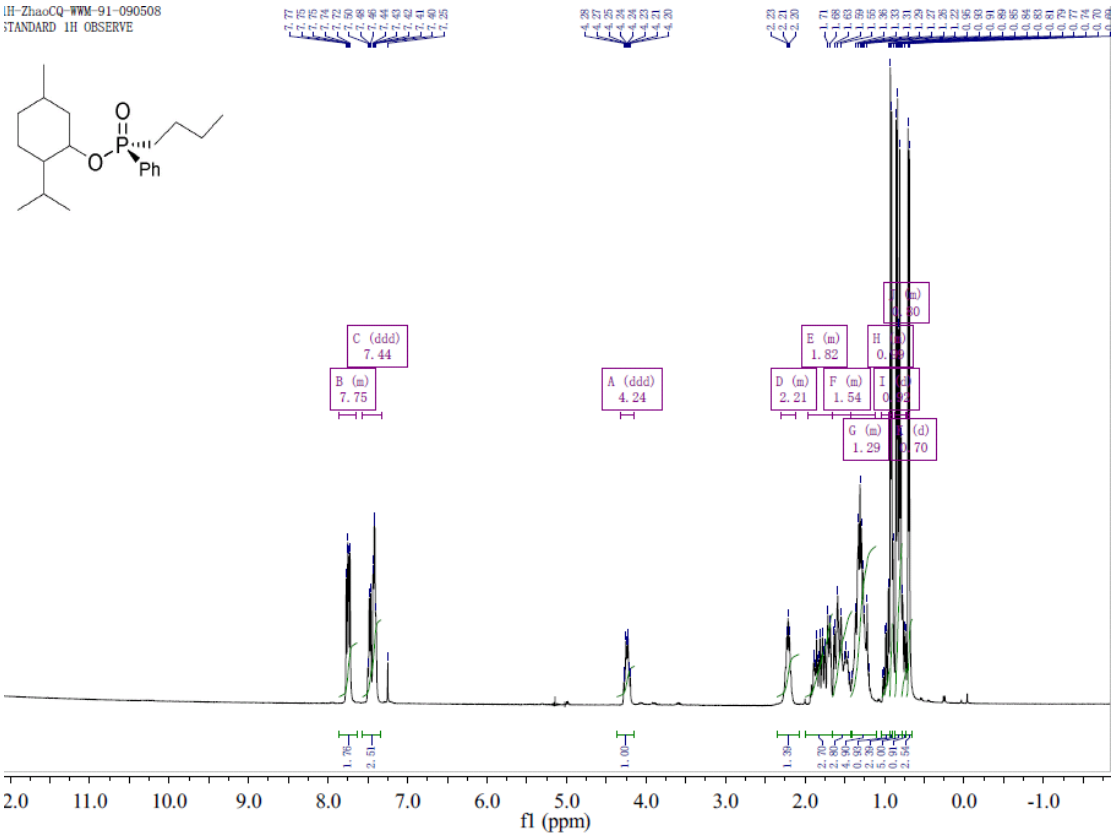
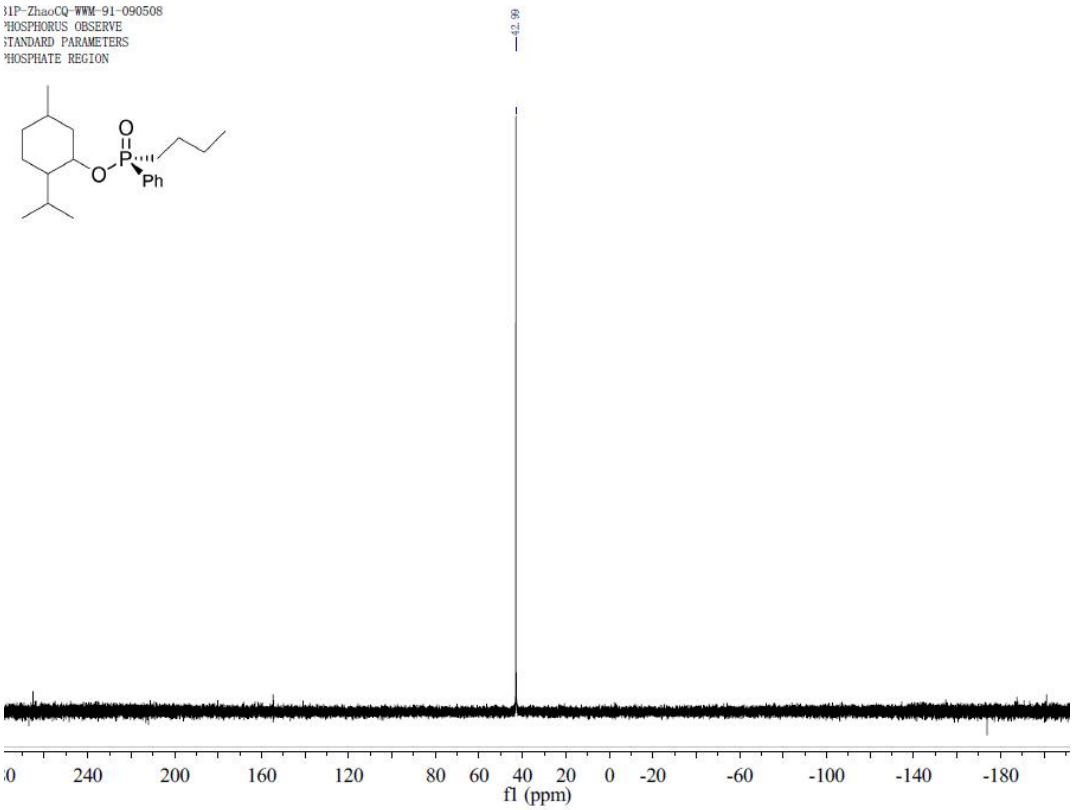


(R_P)-*O*-Menthyl *n*-butylphenylphosphinate (12c')



(R_P)-*O*-Menthyl *n*-butylphenylphosphinate (12c')



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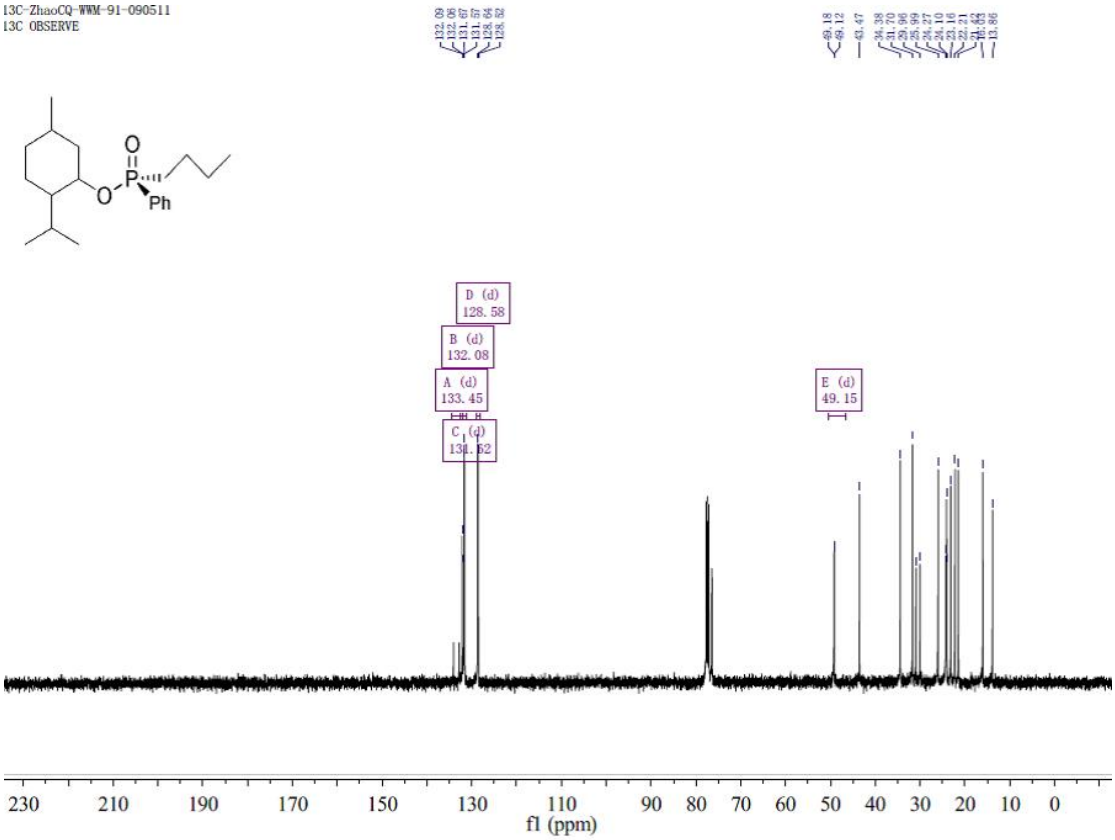
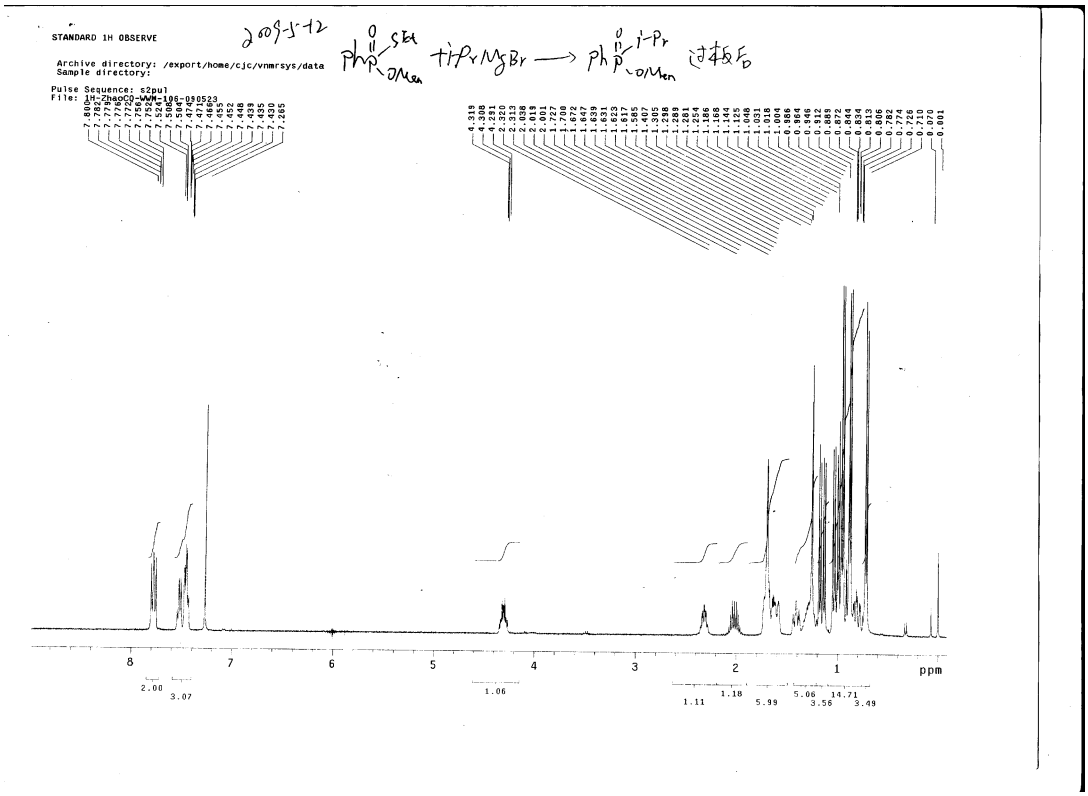
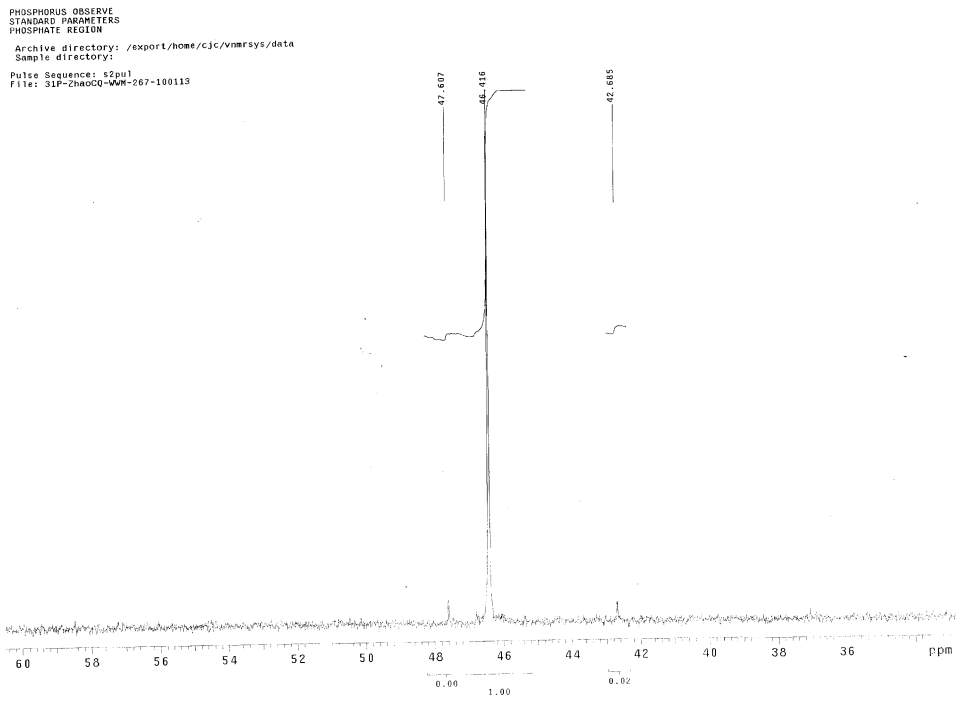


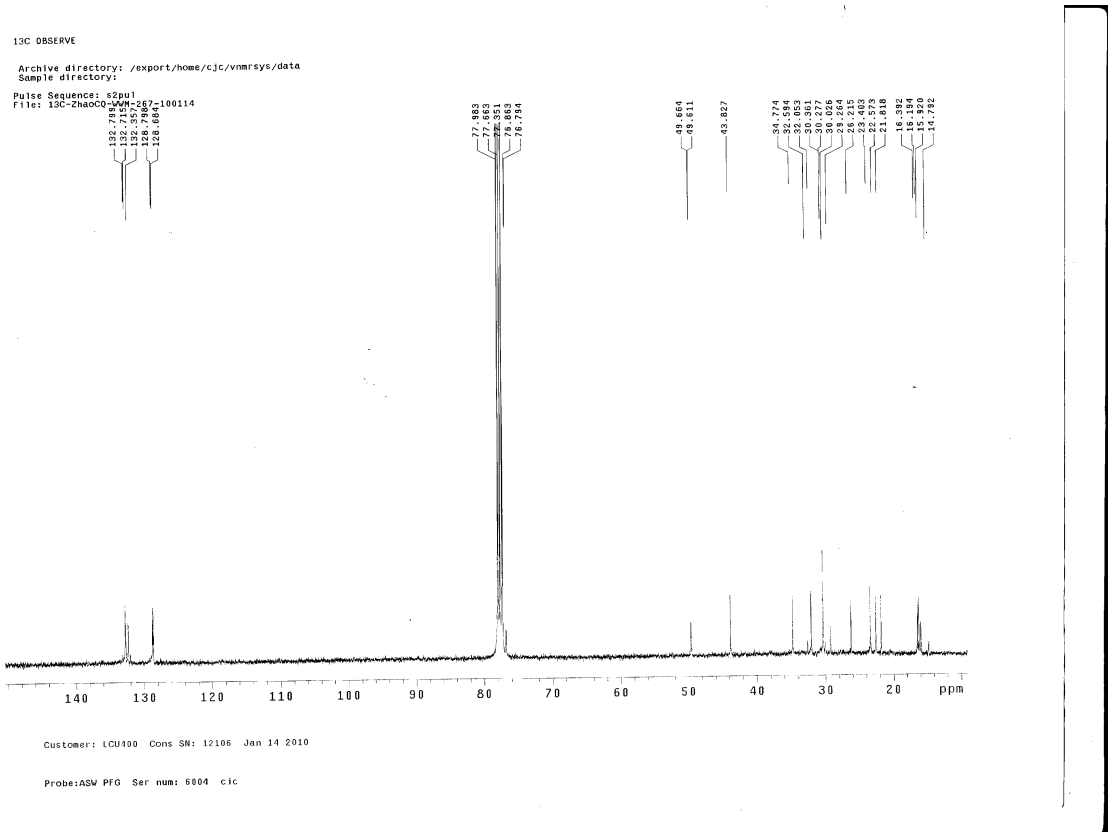
(R_P)-*O*-Menthyl *i*-propylmethylphenylphosphinate (12d')



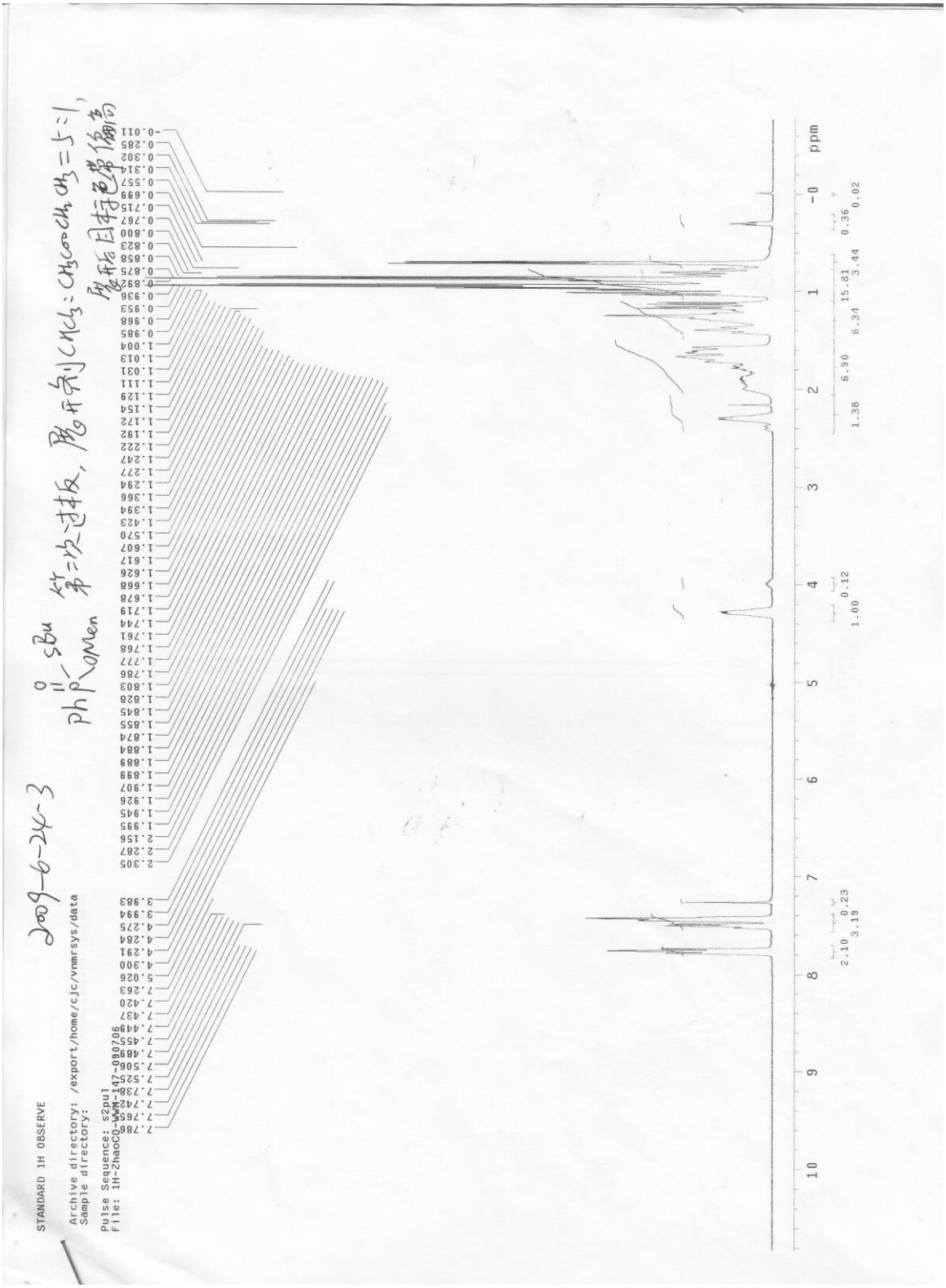
(R_P)-*O*-Menthyl *i*-propylmethylphenylphosphinate (12d')



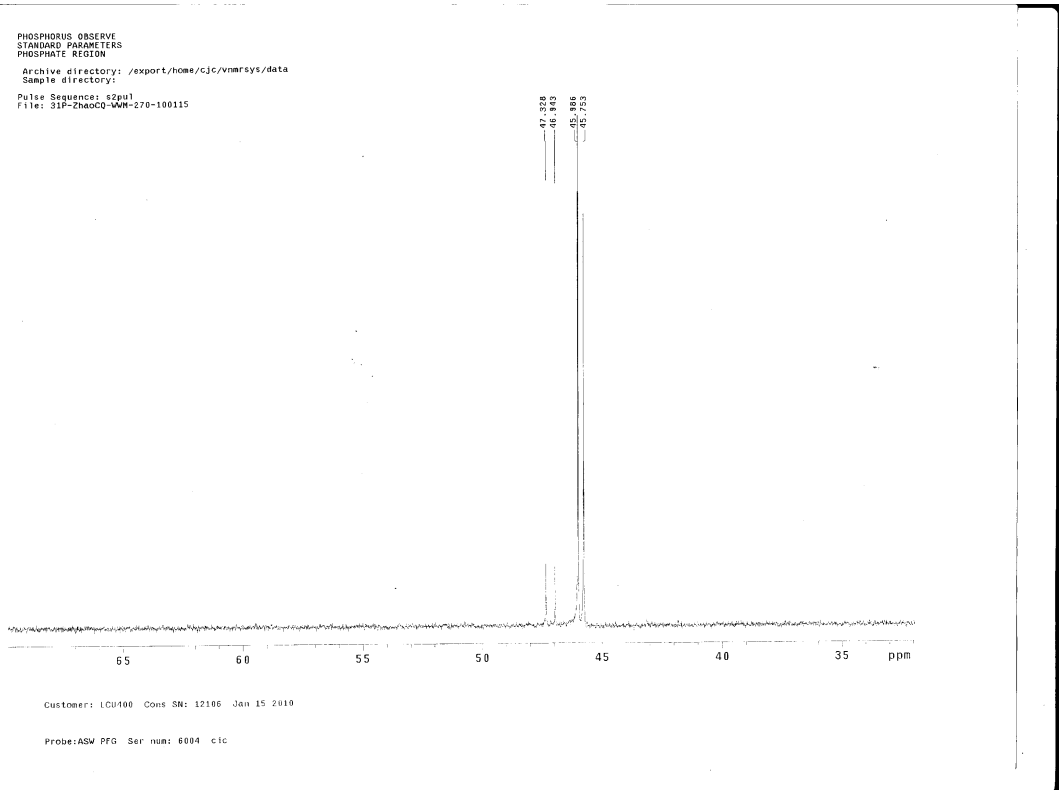
(R_P)-*O*-Menthyl *i*-propylmethylphenylphosphinate (12d')



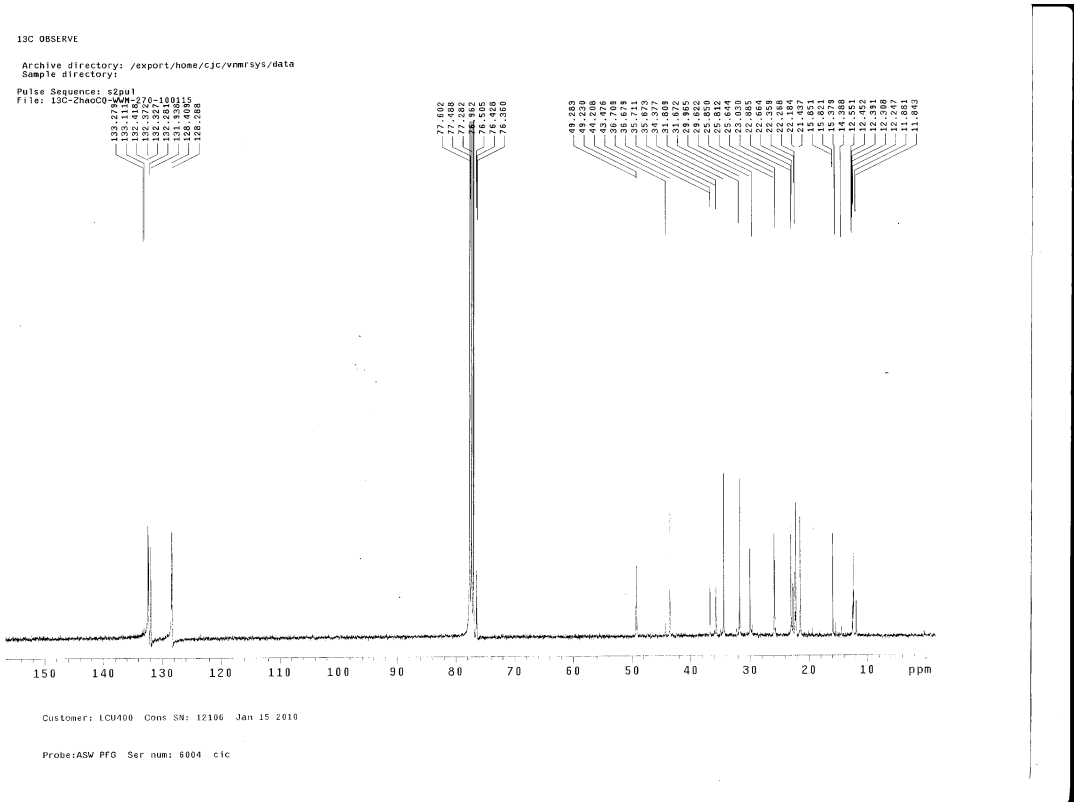
(R_P)-*O*-Menthyl *s*-butylphenylphosphinate (12f')



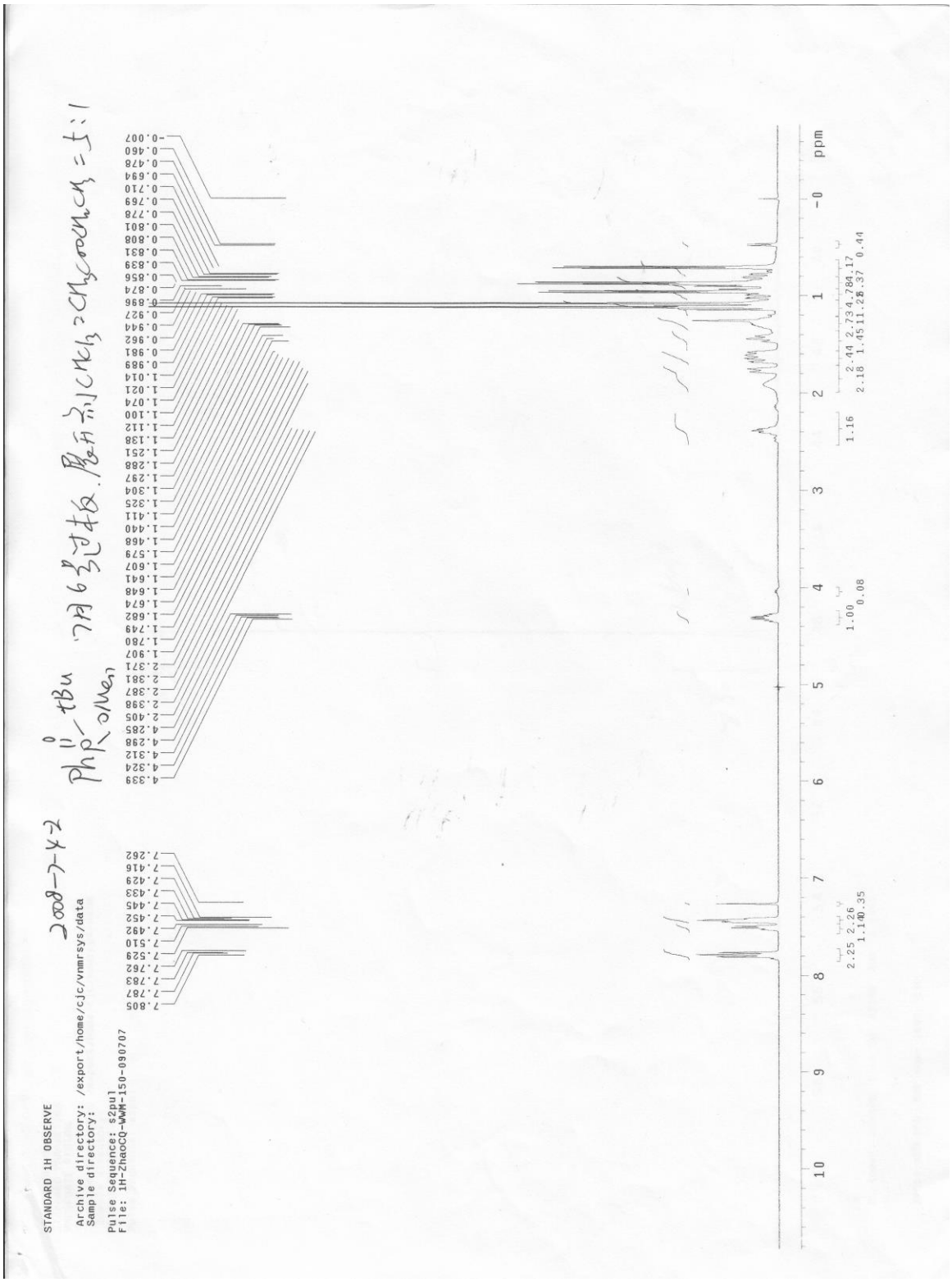
(*R*P)-*O*-Menthyl *s*-butylphenylphosphinate (12f')



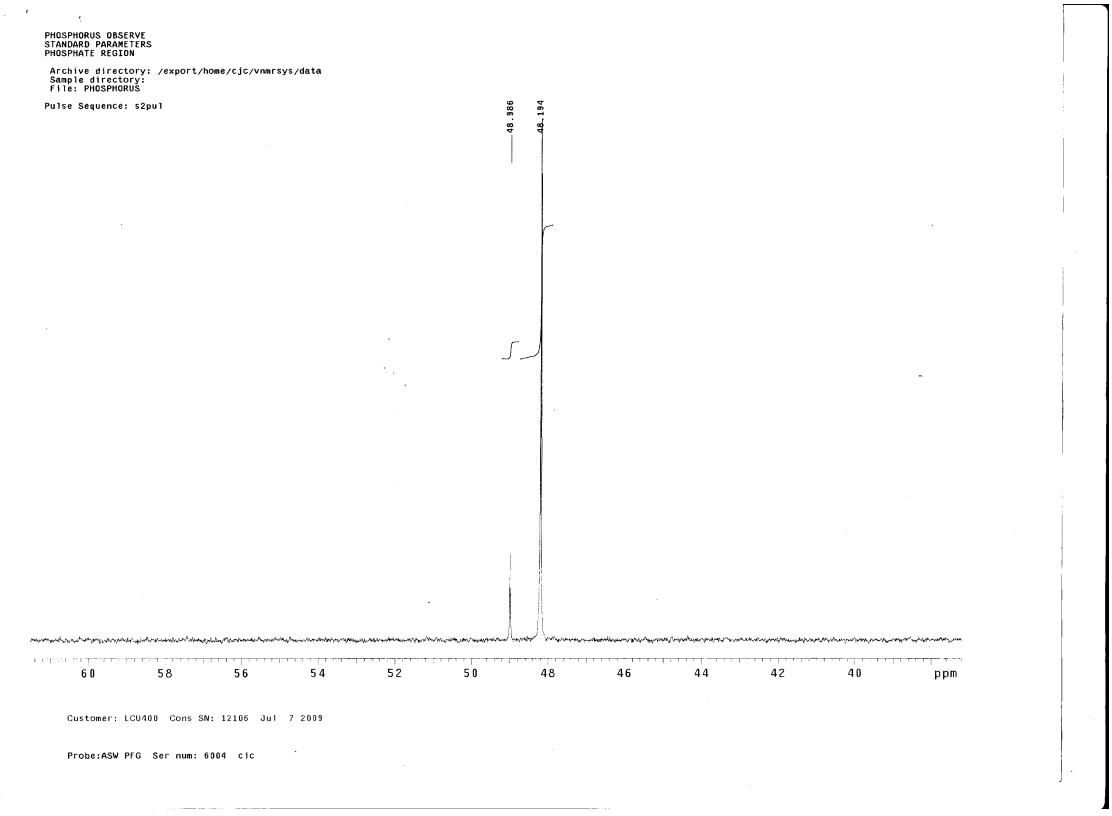
(*R*P)-*O*-Menthyl *s*-butylphenylphosphinate (12f')



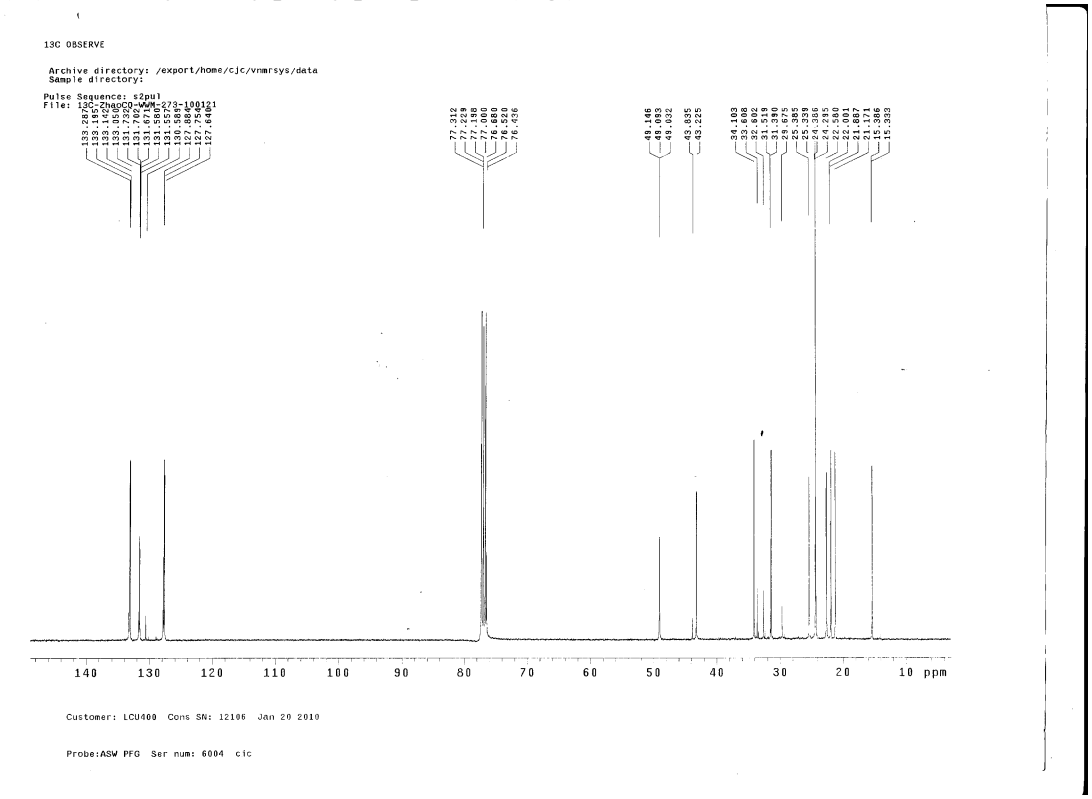
(R_P)-*O*-Menthyl *t*-butylphenylphosphinate (12g')



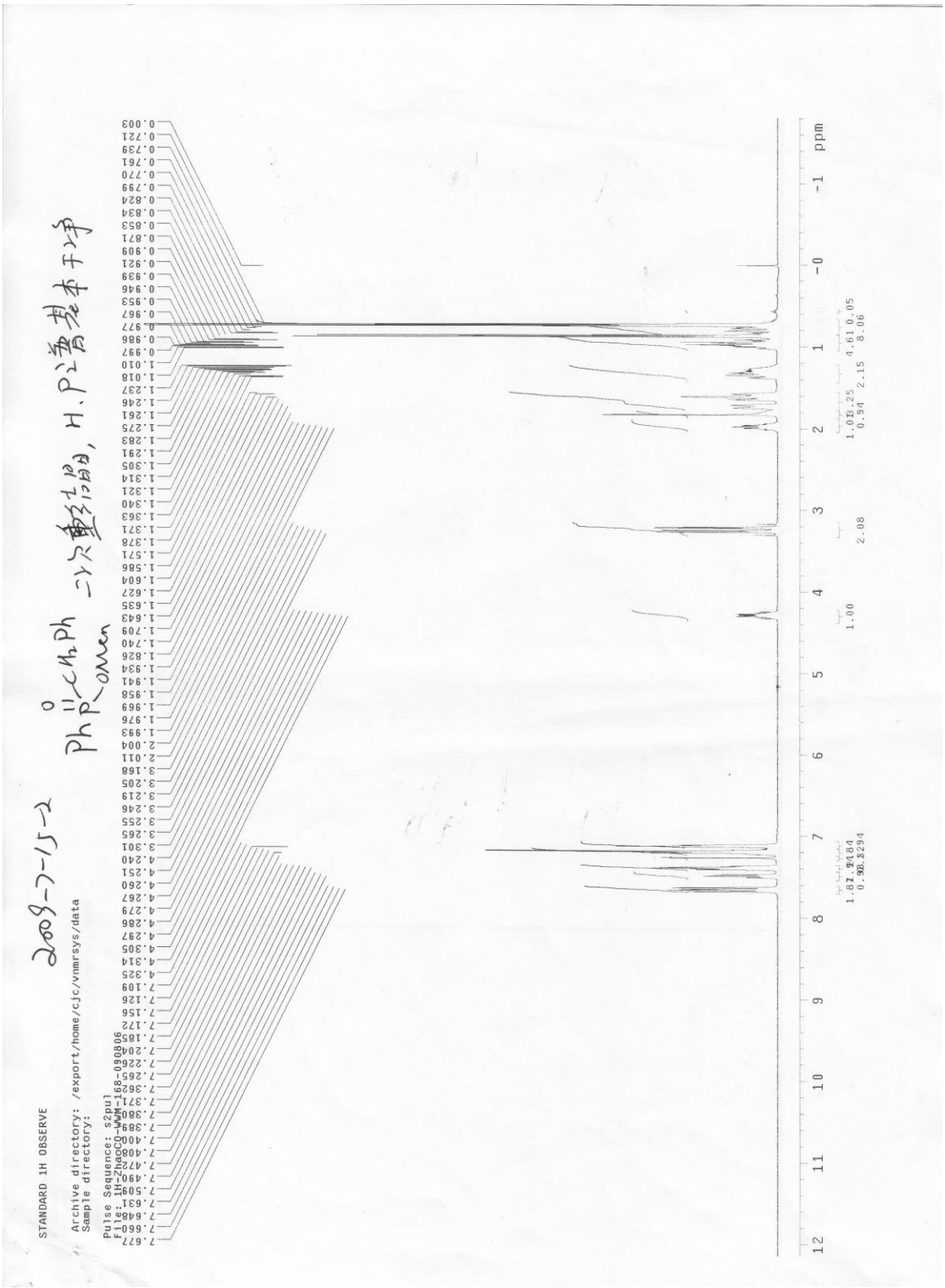
(S_P)-*O*-Menthyl *t*-butylphenylphosphinate (12g')



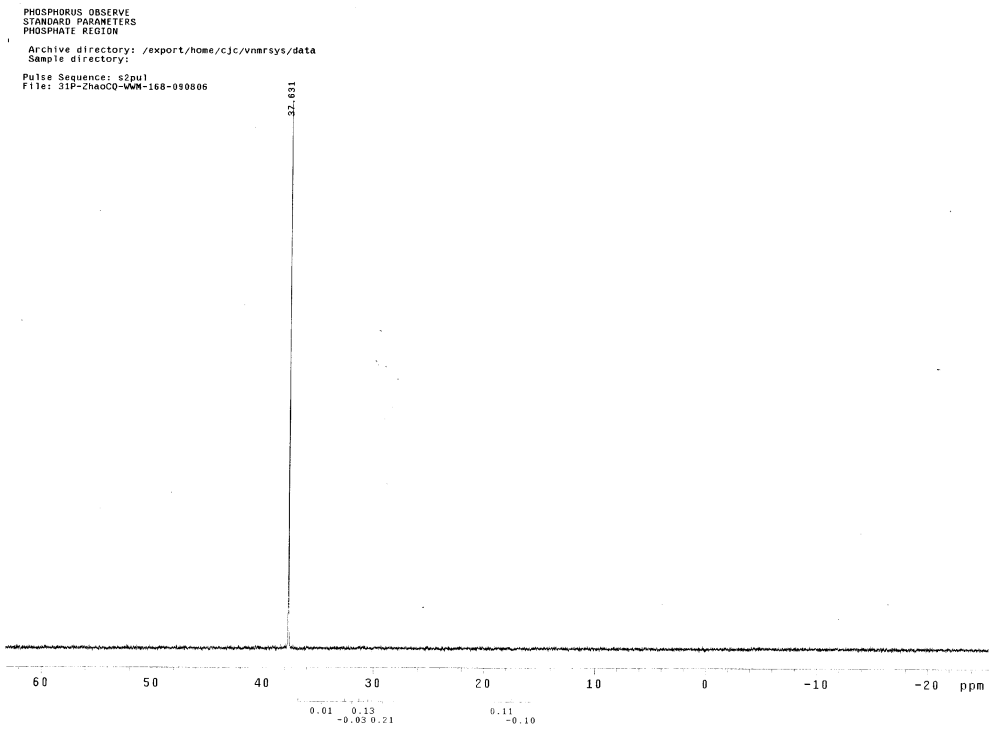
(S_P)-*O*-Menthyl *t*-butylphenylphosphinate (12g')



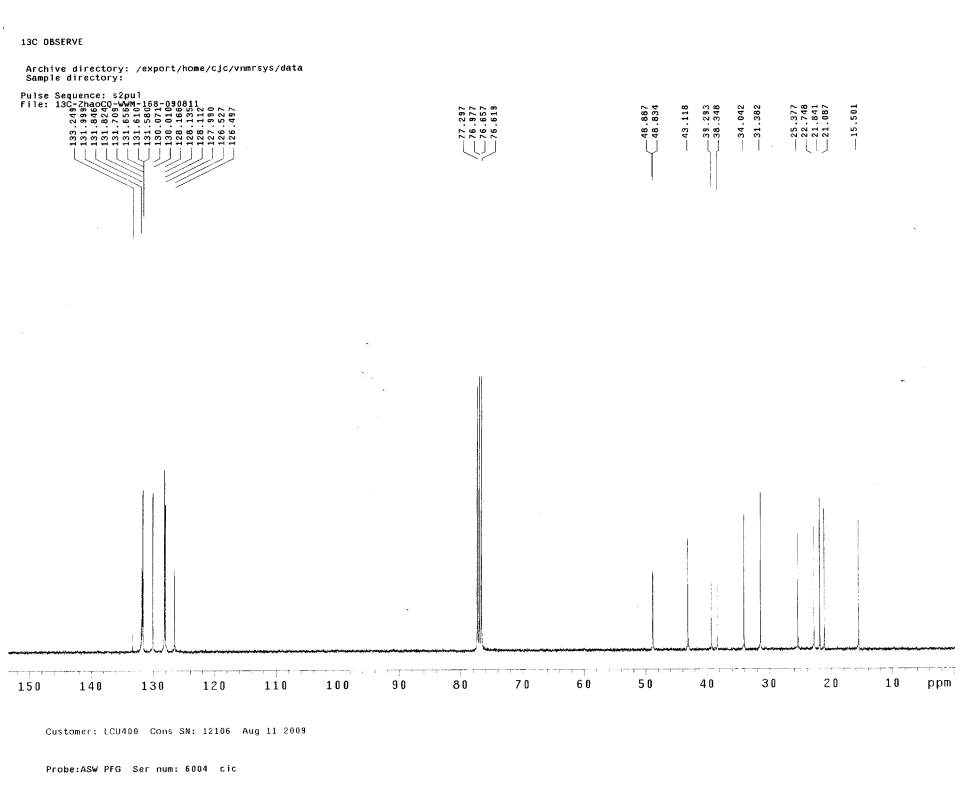
(S_P)-*O*-Menthyl benzylphenylphosphinate (12h')



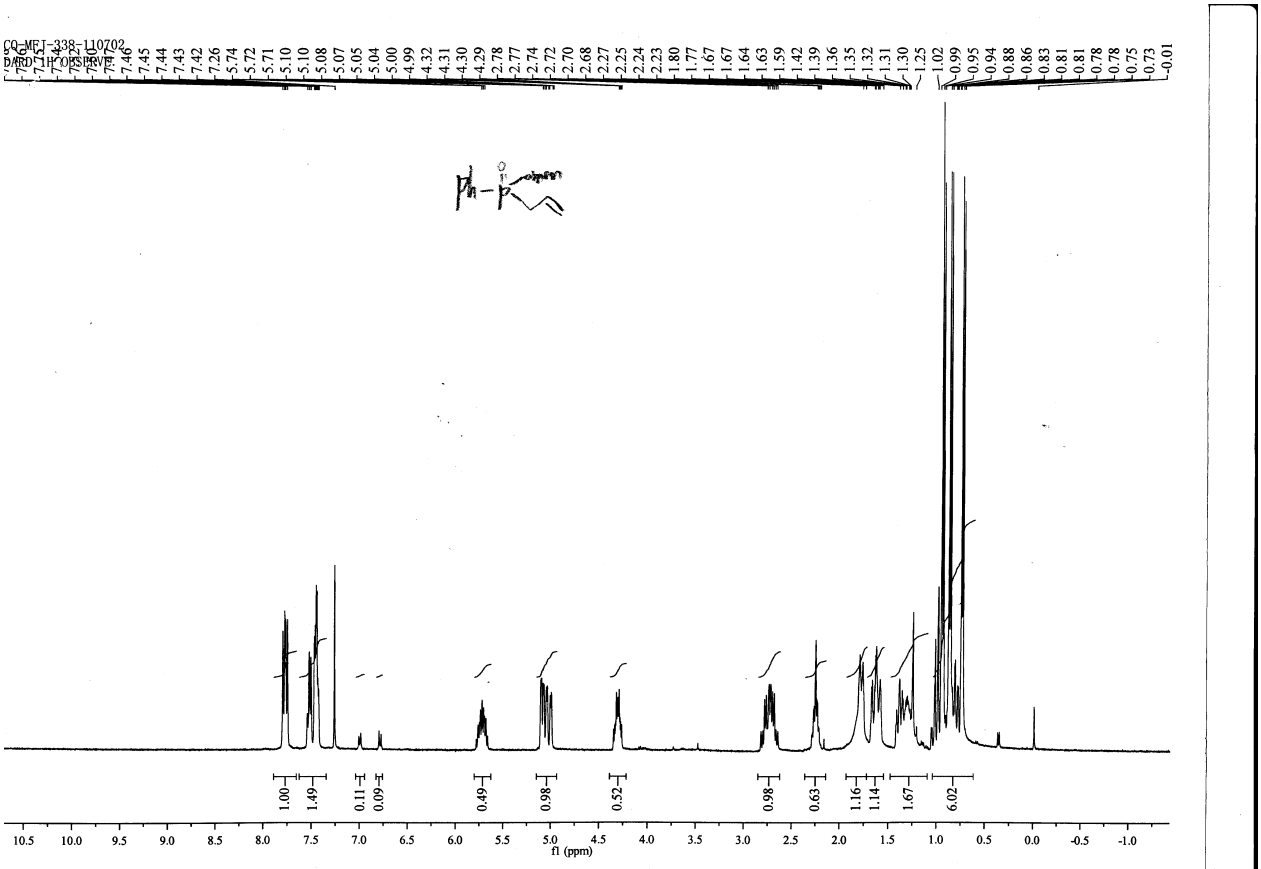
(S_P)-*O*-Menthyl benzylphenylphosphinate (12h')



(R_P)-*O*-Menthyl benzylphenylphosphinate (12h')



(R_P)-*O*-Menthyl allylphenylphosphinate (12i')



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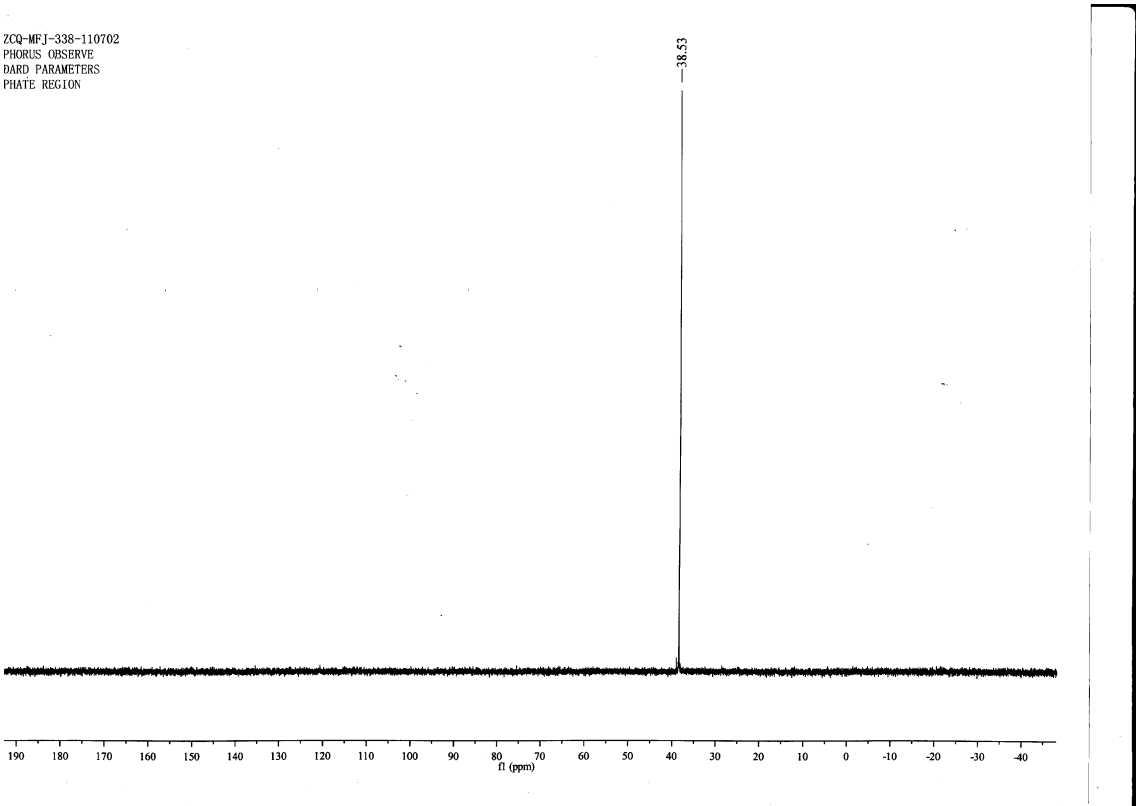
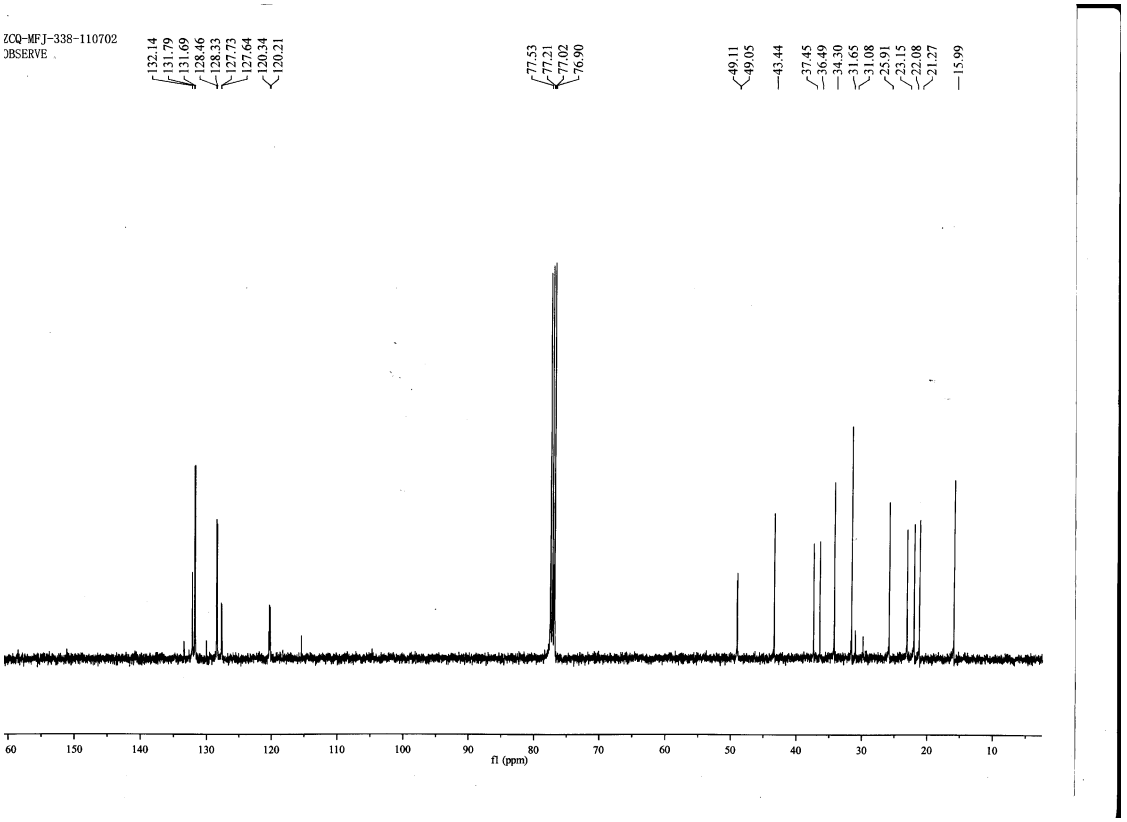
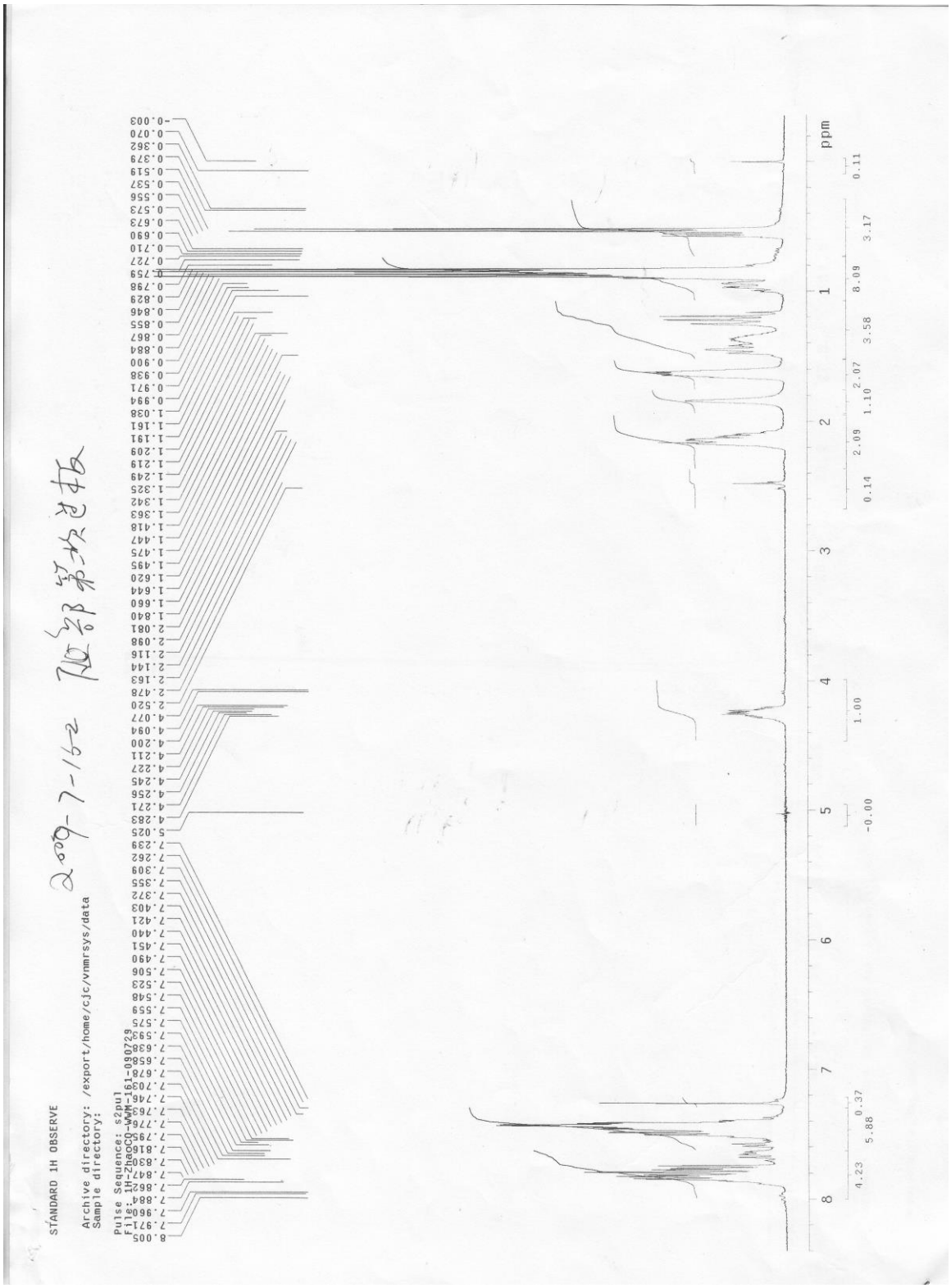


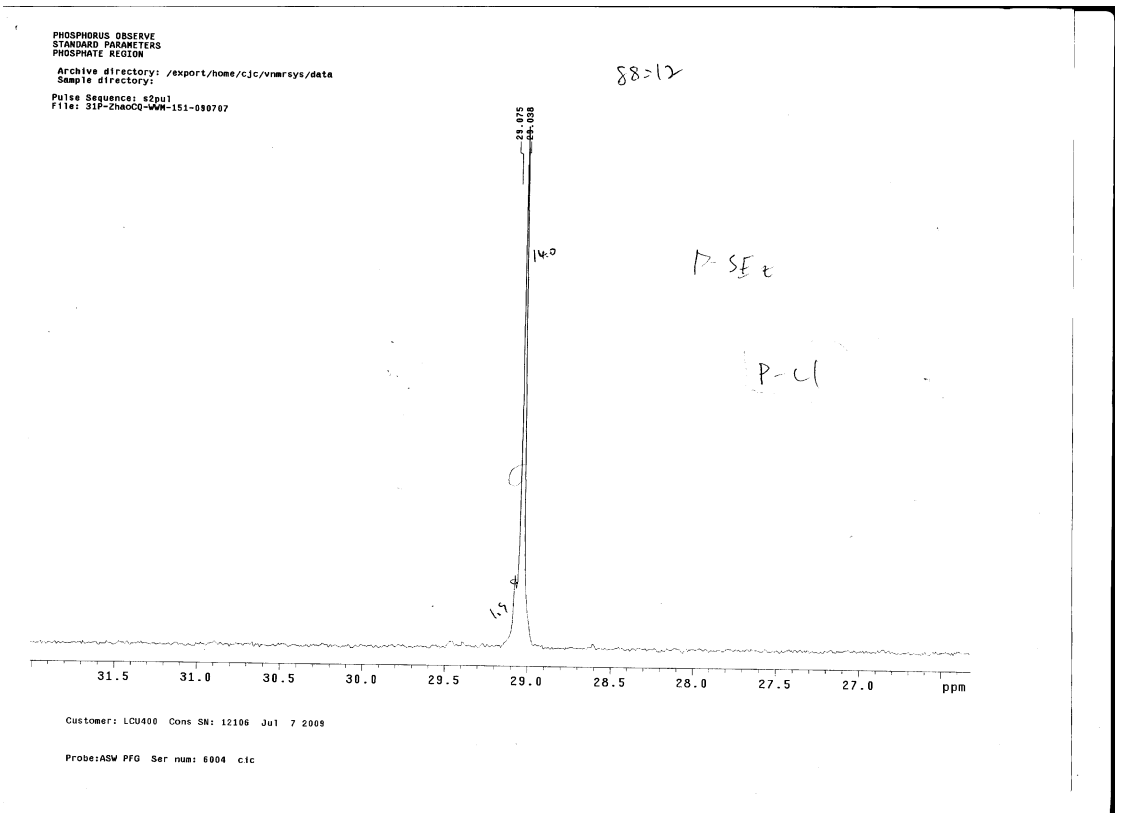
(R_P)-*O*-Menthyl allylphenylphosphinate (12i')



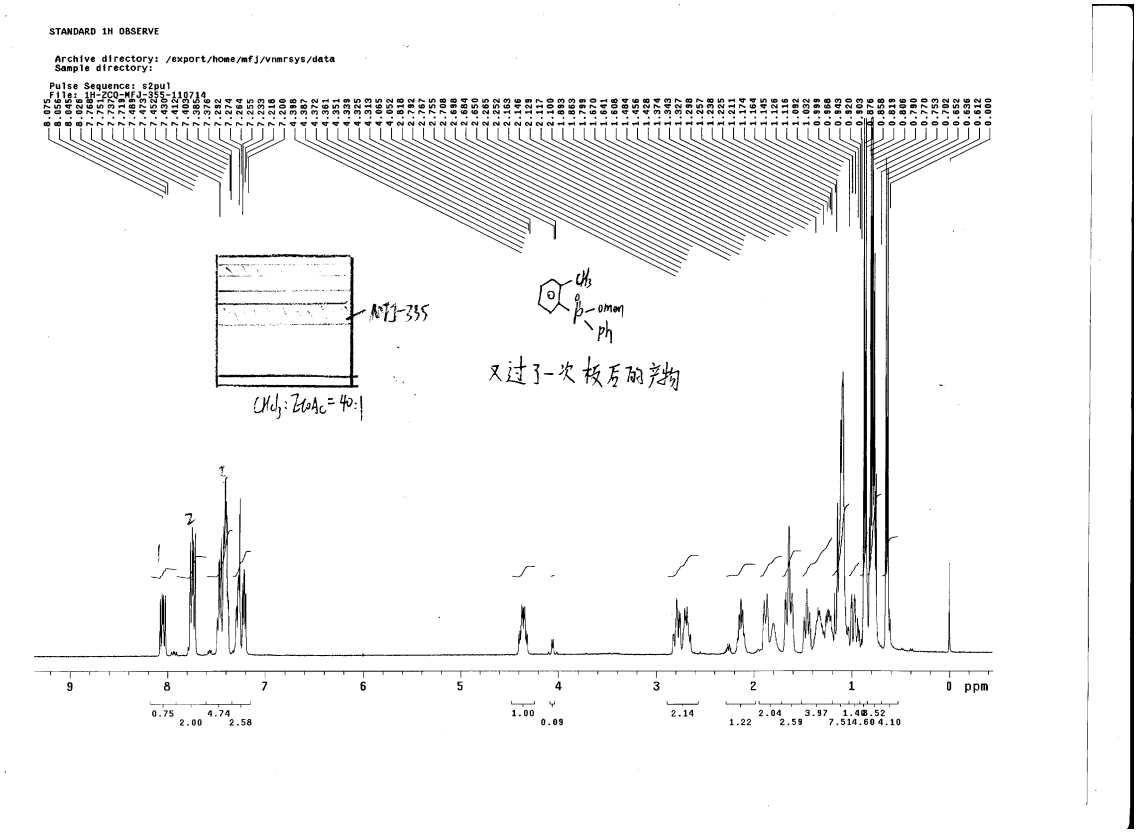
(S_P)-*O*-Menthyl *p*-bromophenylphenylphosphinate (12j')



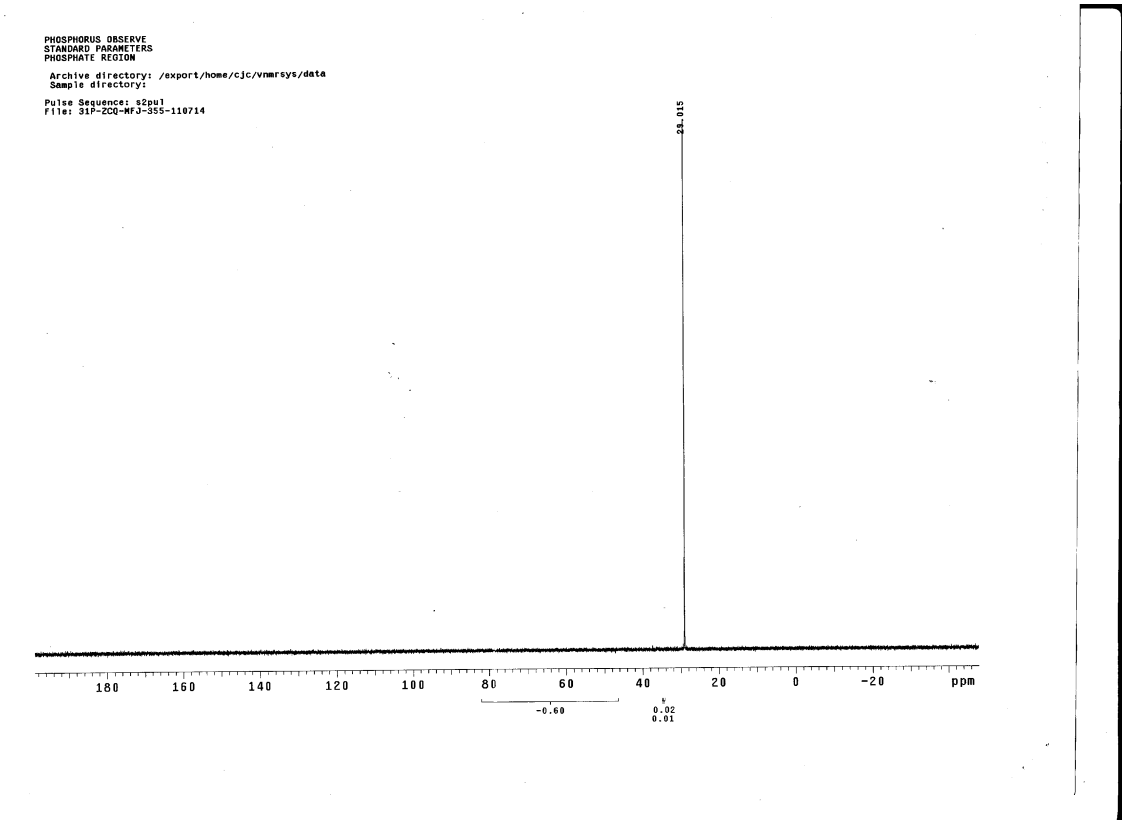
(S_P)-*O*-Menthyl *p*-bromophenylphenylphosphinate (12j')



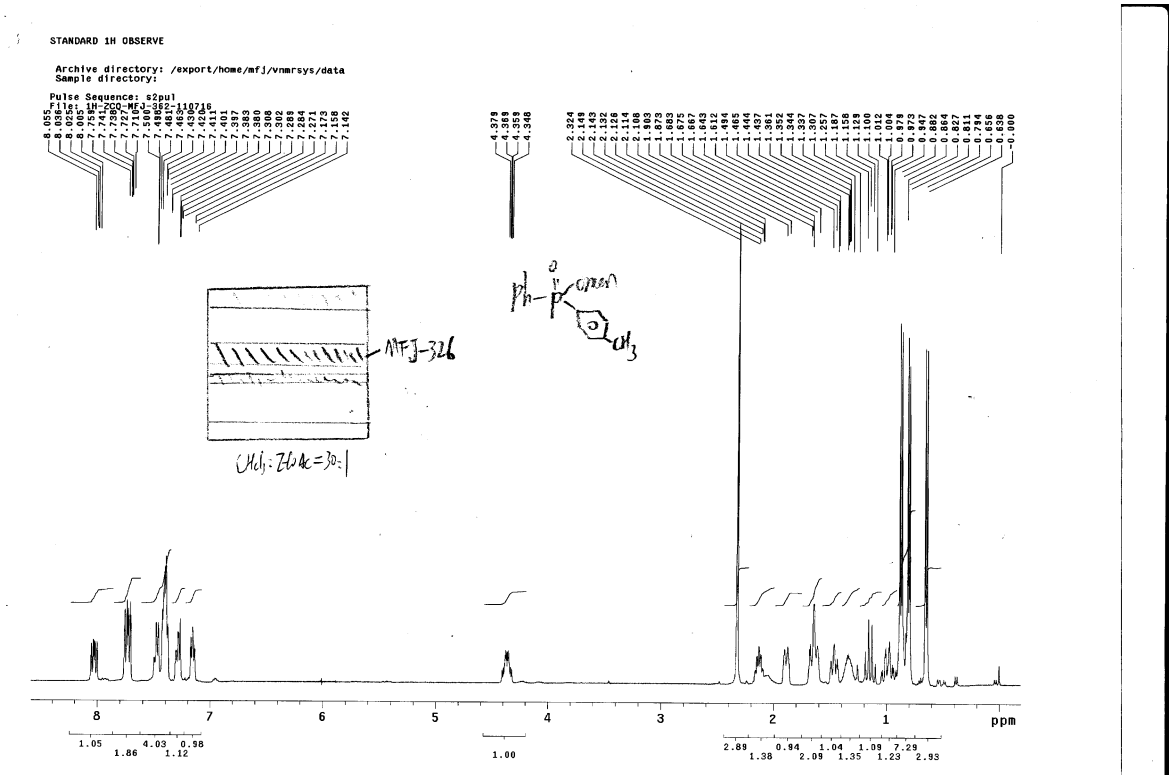
(S_P)-*O*-Menthyl *o*-methylphenylphenylphosphinate (12l')



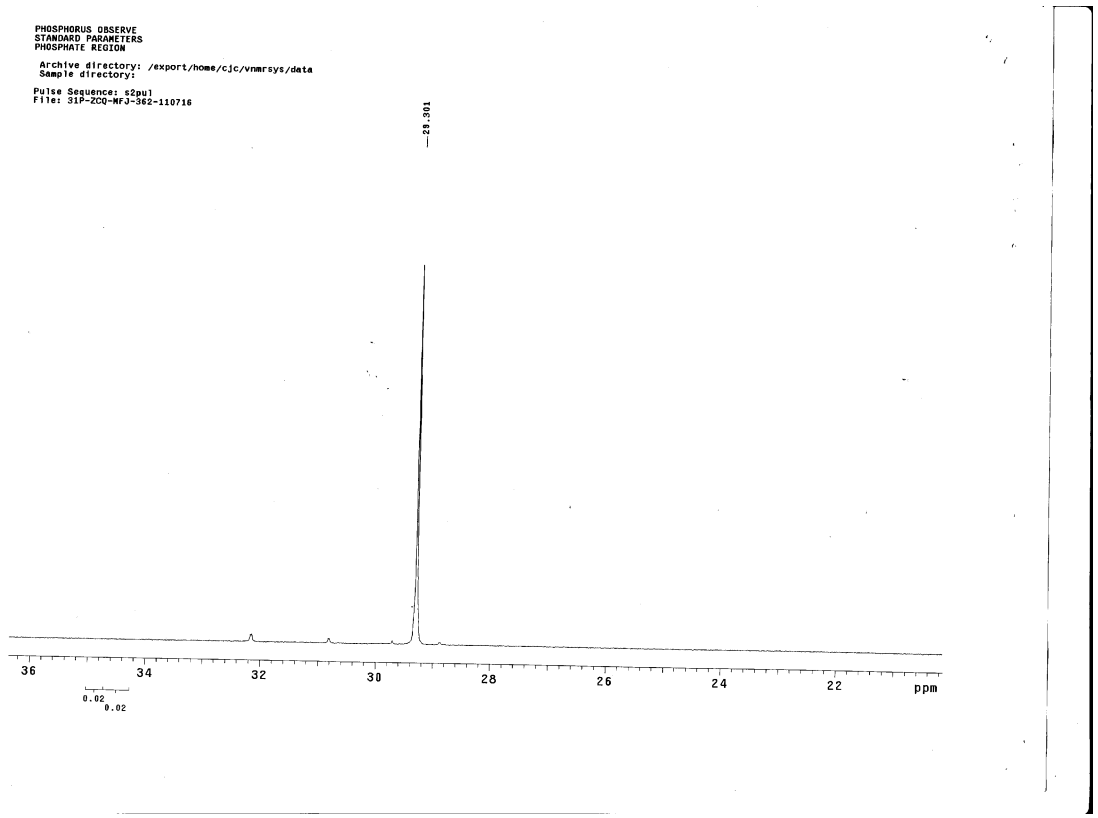
(S_P)-*O*-Menthyl *o*-methylphenylphenylphosphinate (12l')



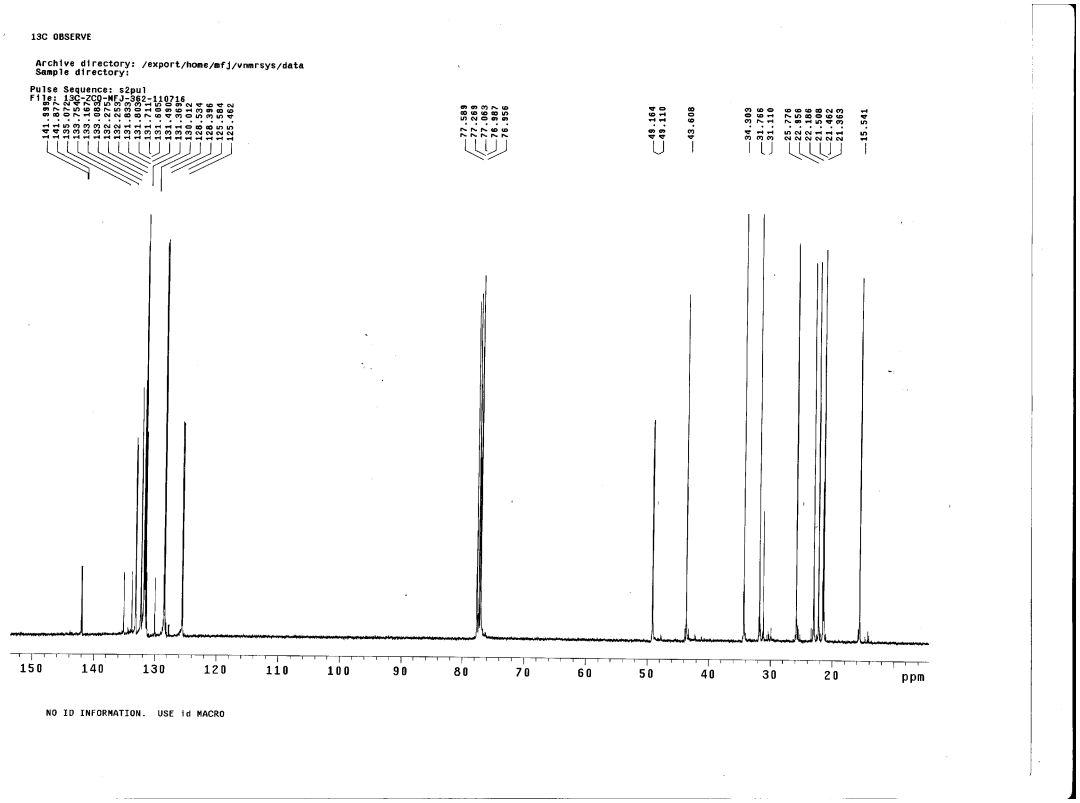
(S_P)-*O*-Menthyl *p*-methylphenylphenylphosphinate (12n')



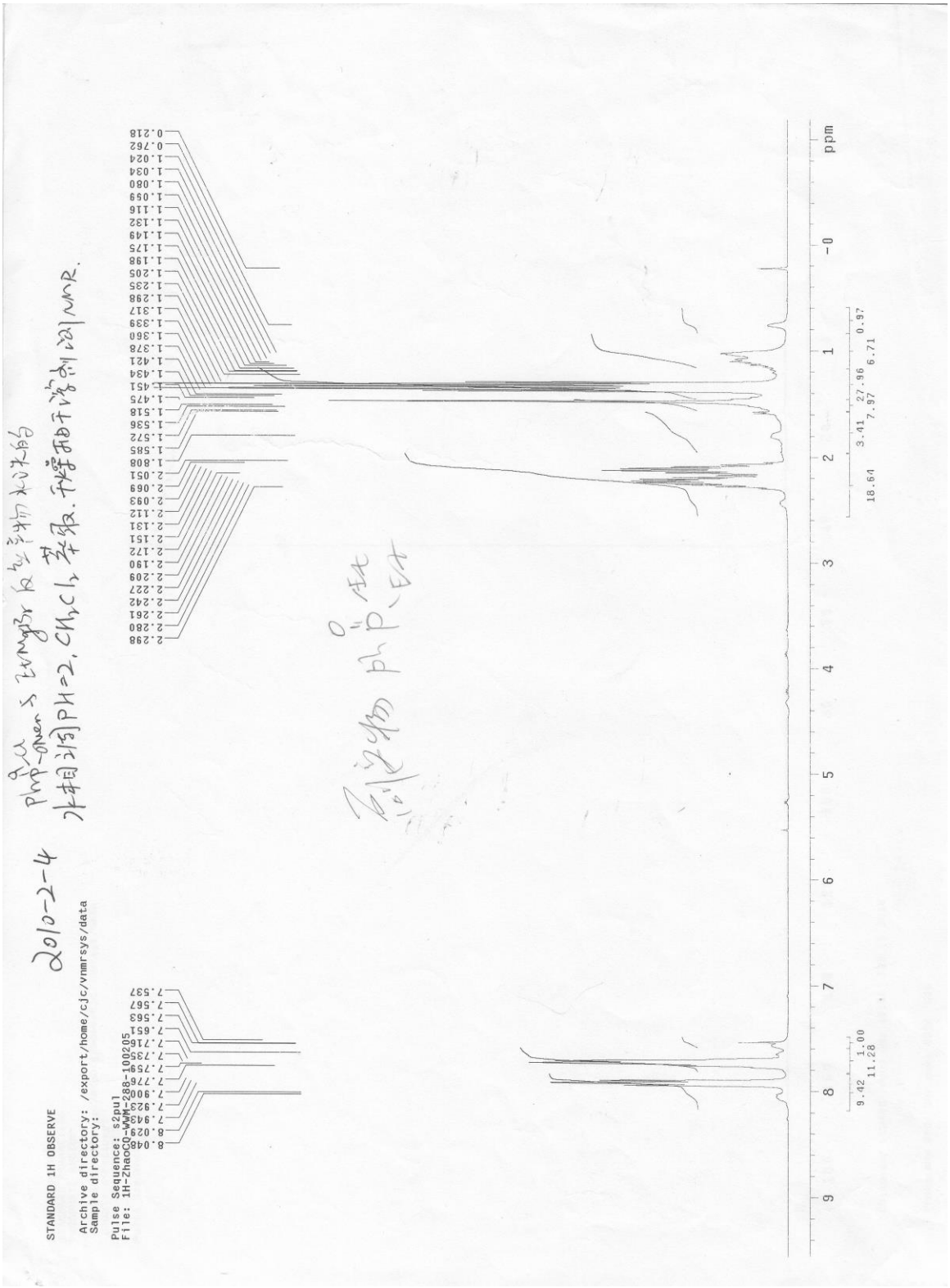
(S_P)-*O*-Menthyl *p*-methylphenylphenylphosphinate (12n')



(S_P)-*O*-Menthyl *p*-methylphenylphenylphosphinate (12n')



Diethyl phenylphosphine oxide 13b



Diethyl phenylphosphine oxide 13b