Staudinger Ligation of Peptides at Non-Glycyl Residues

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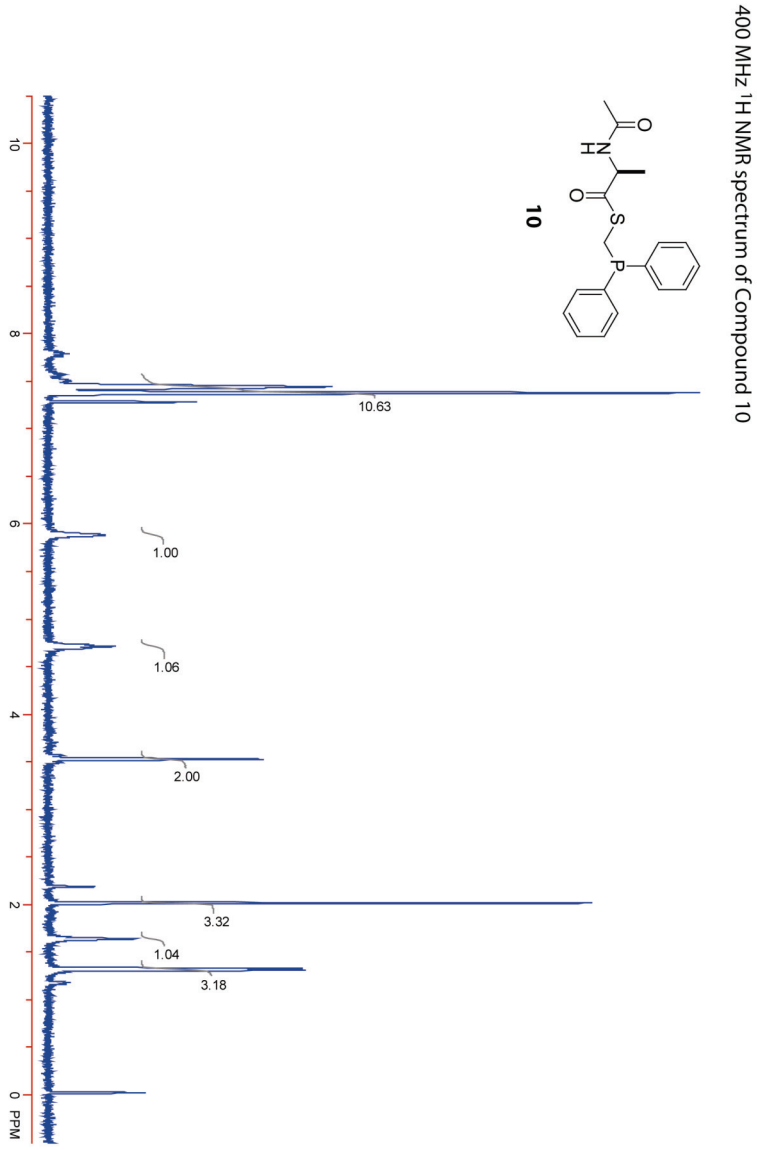
General Experimental Procedures

General Materials. Reagent chemicals were obtained from commercial suppliers, and reagent-grade solvents were used without further purification. Reactions were performed at room temperature, and were monitored by thin-layer chromatography with visualization by UV light or staining with ninhydrin or I_2. Compounds were purified with an Argonaut Flashmaster Solo automated chromatography system unless indicated otherwise. Silica gel used in flash chromatography had 230–400 mesh and 60-Å pore size.

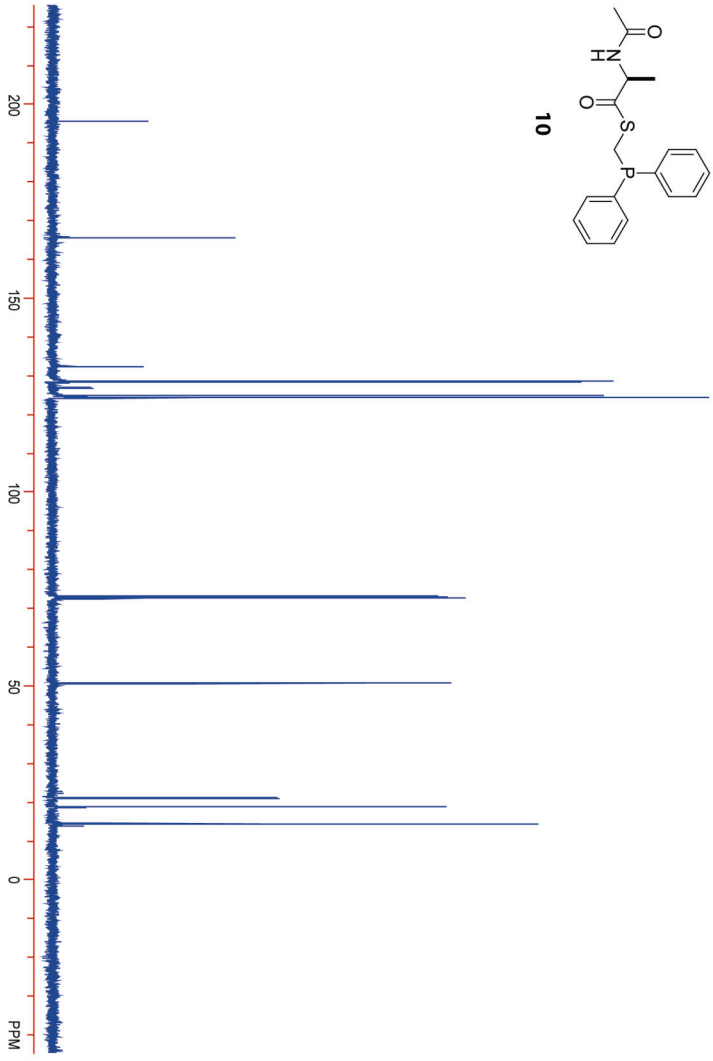
General Methods. The removal of solvent "under reduced pressure" refers to the use of a rotary evaporator at water aspirator pressure (<20 torr) while maintaining the water-bath temperature below 40 °C. Residual DMF was removed from samples at high vacuum (<0.1 torr) by the use of a mechanical belt-drive oil pump.

NMR Spectroscopy and Mass Spectrometry. NMR spectra were obtained with a 500 or 400 MHz spectrometer at the National Magnetic Resonance Facility at Madison or the University of Wisconsin Nuclear Magnetic Resonance Facility, respectively. Carbon-13 and phosphorus-31 spectra were both proton-decoupled, and phosphorus-31 spectra were referenced against an external standard of deuterated phosphoric acid (0 ppm). Mass spectra were obtained with electrospray ionization (ESI) techniques.

General Procedures for Staudinger Ligations. Unless noted otherwise, Staudinger ligations were performed at room temperature with equimolar amounts of phosphinothioester (or phosphinoester) and azide (0.105 mmol) in a solvent (600 μL). Solvents were not degassed, and ligations were performed under air.

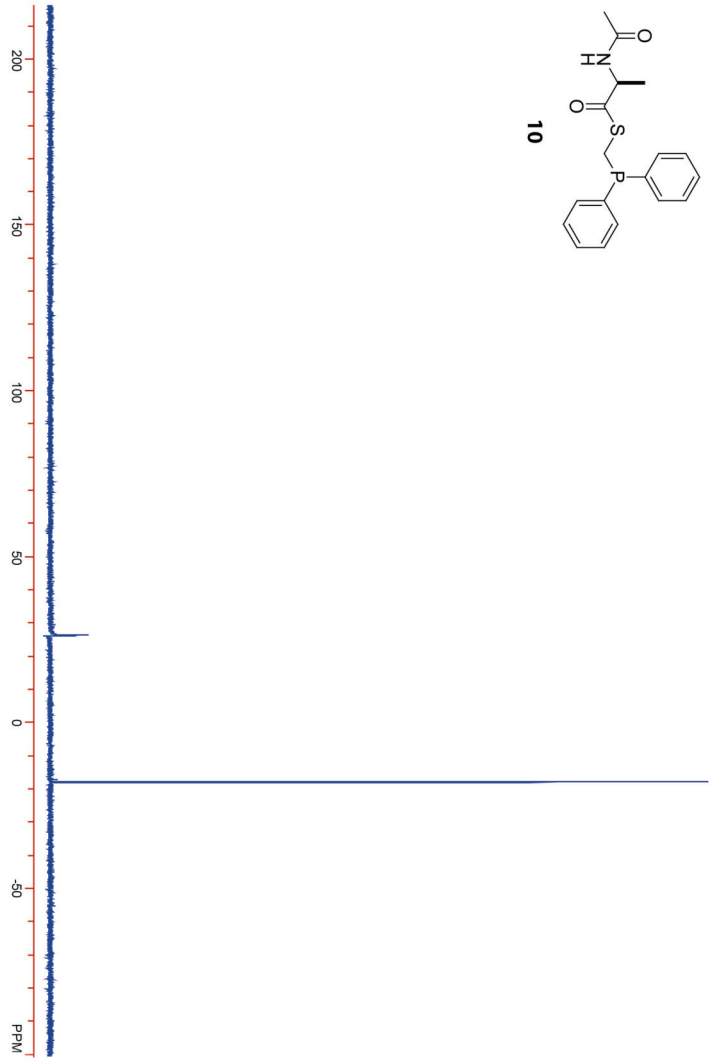

400 MHz ^{1}H NMR spectrum of Compound 10
10
10.63
1.00
1.06
2.00
3.32
1.04
3.18
10
8
6
4
2
0 PPM

125 MHz ^{13}C NMR spectrum of Compound 10



10

161 MHz ^{31}P NMR spectrum of Compound 10



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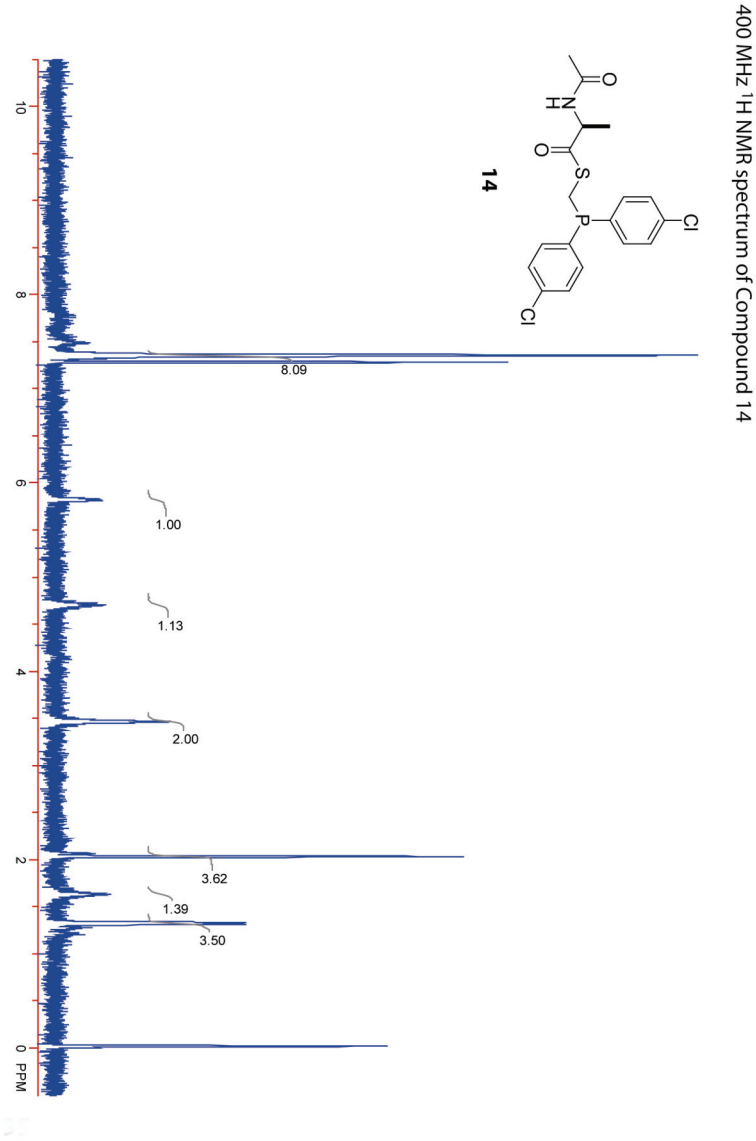
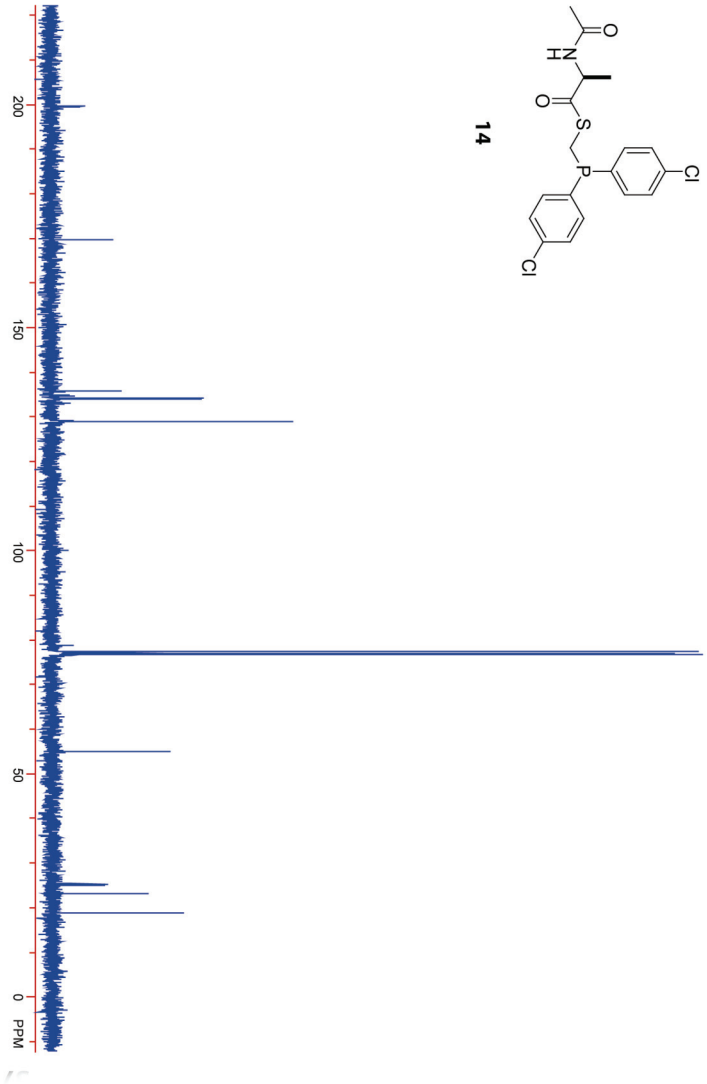

400 MHz ¹H NMR spectrum of Compound 14
14
8.09
1.00
1.13
2.00
3.62
1.39
3.50
PPM

125 MHz ^{13}C NMR spectrum of Compound 14



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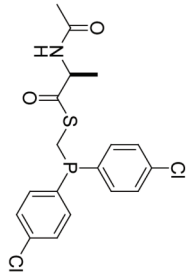
161 MHz ^{31}P NMR spectrum of Compound 14



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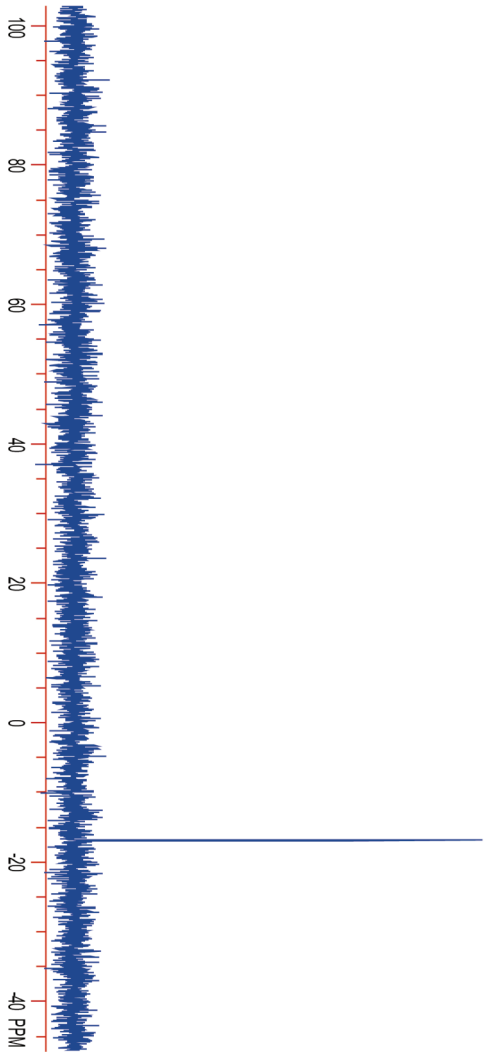
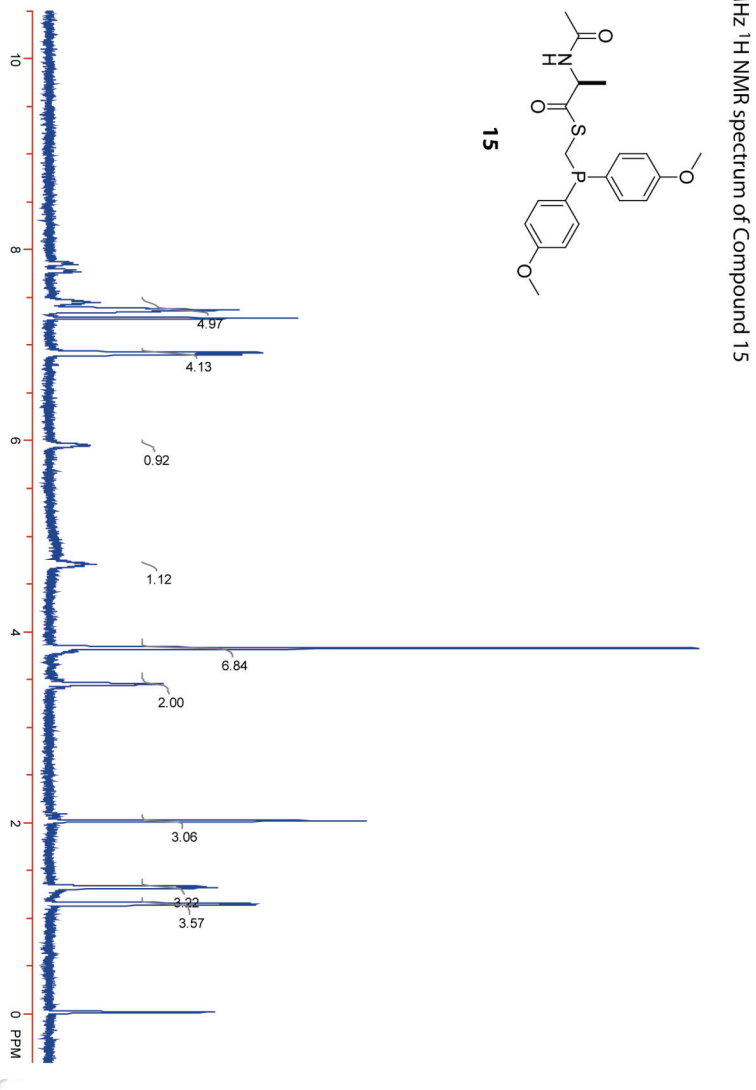
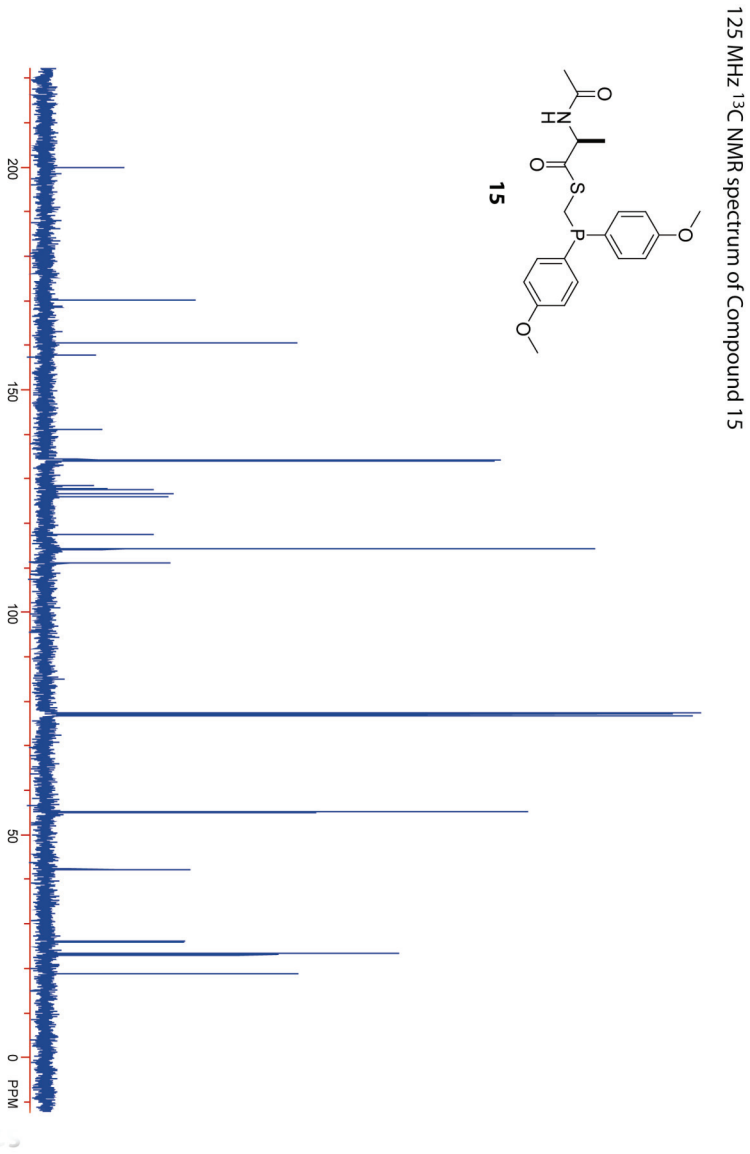
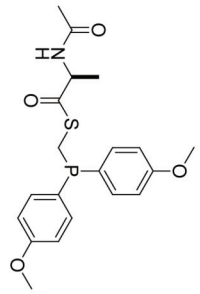


400 MHz ^{1}H NMR spectrum of Compound 15



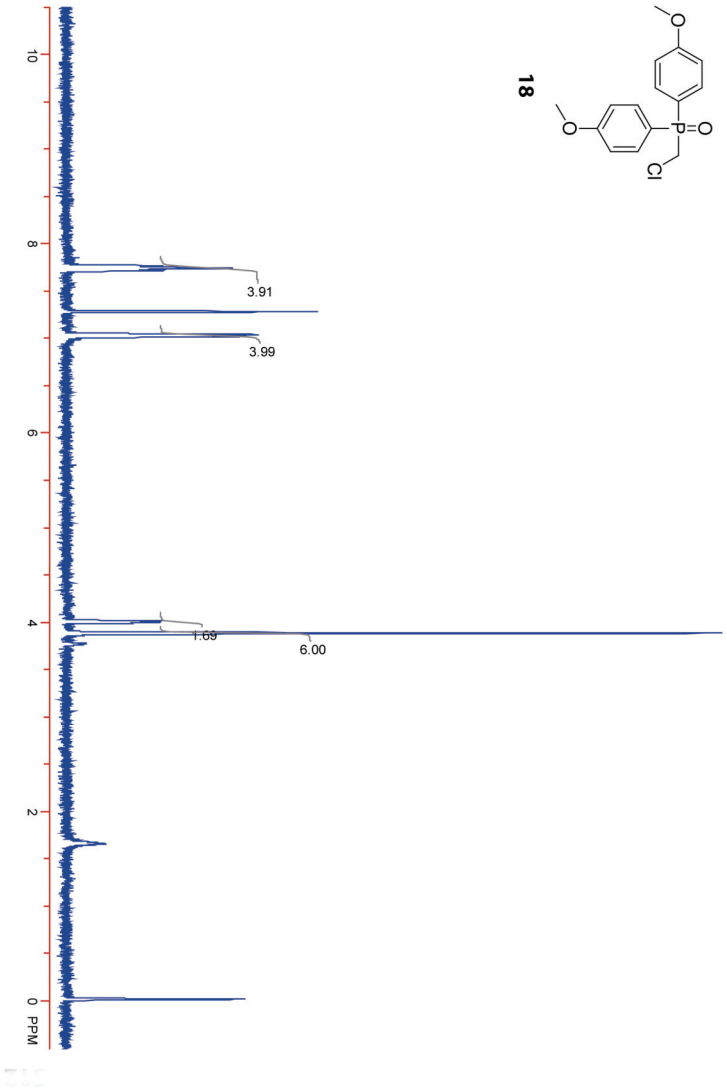

125 MHz ^{13}C NMR spectrum of Compound 15
15
200
150
100
50
0
PPM

161 MHz ^{31}P NMR spectrum of Compound 15

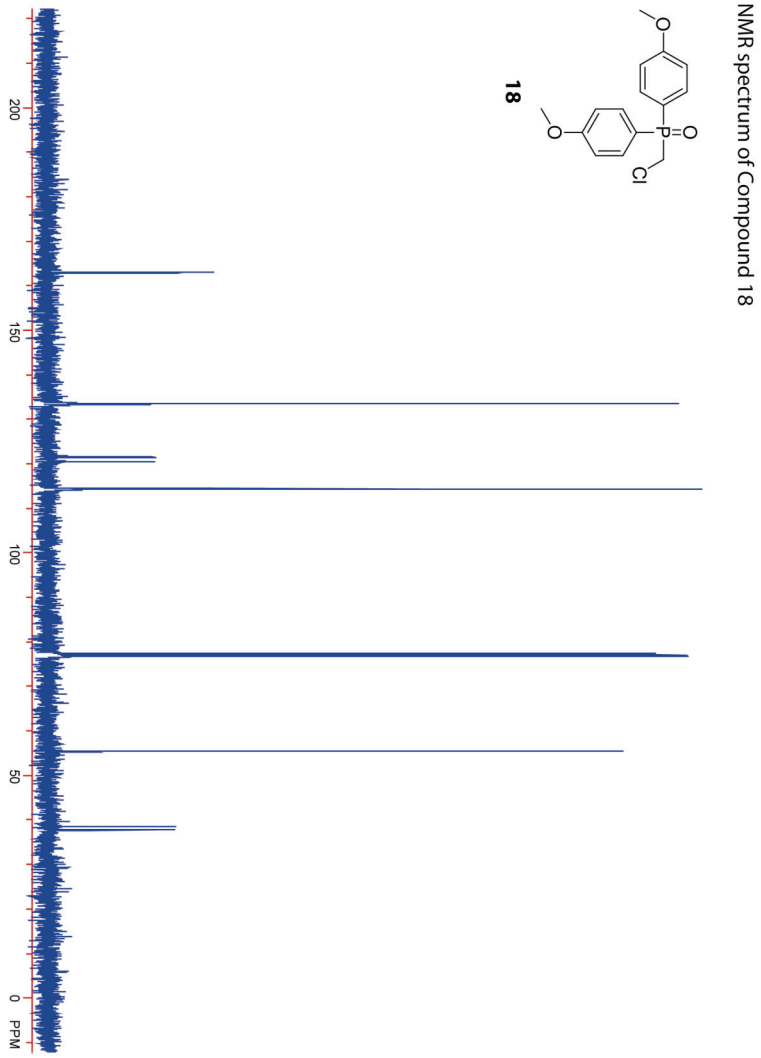


15

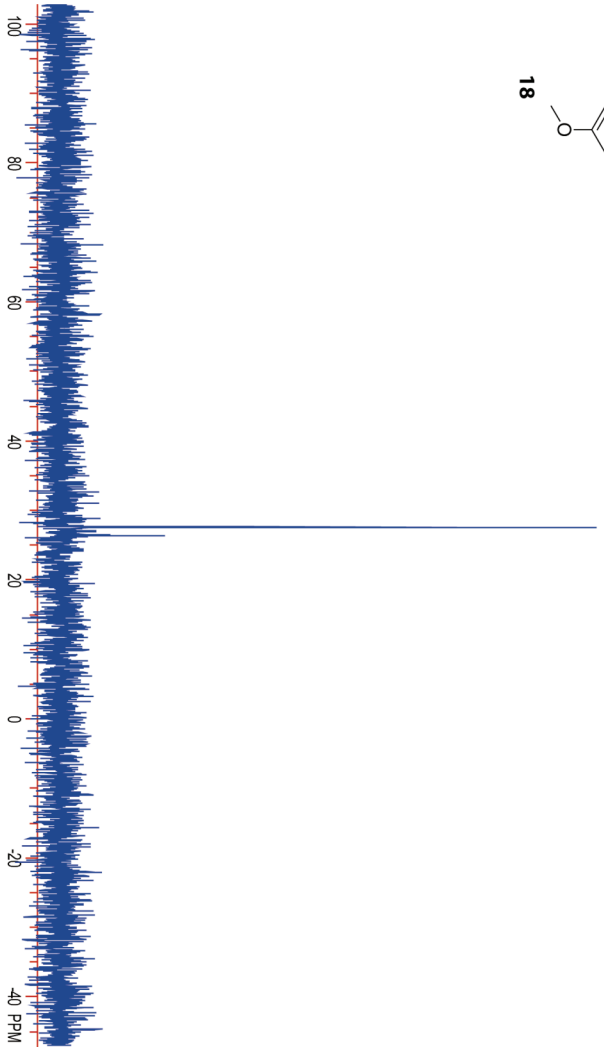
400 MHz ^{1}H NMR spectrum of Compound 18



125 MHz ^{13}C NMR spectrum of Compound 18



161 MHz ^{31}P NMR spectrum of Compound 18



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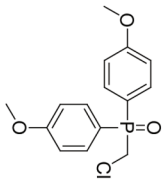
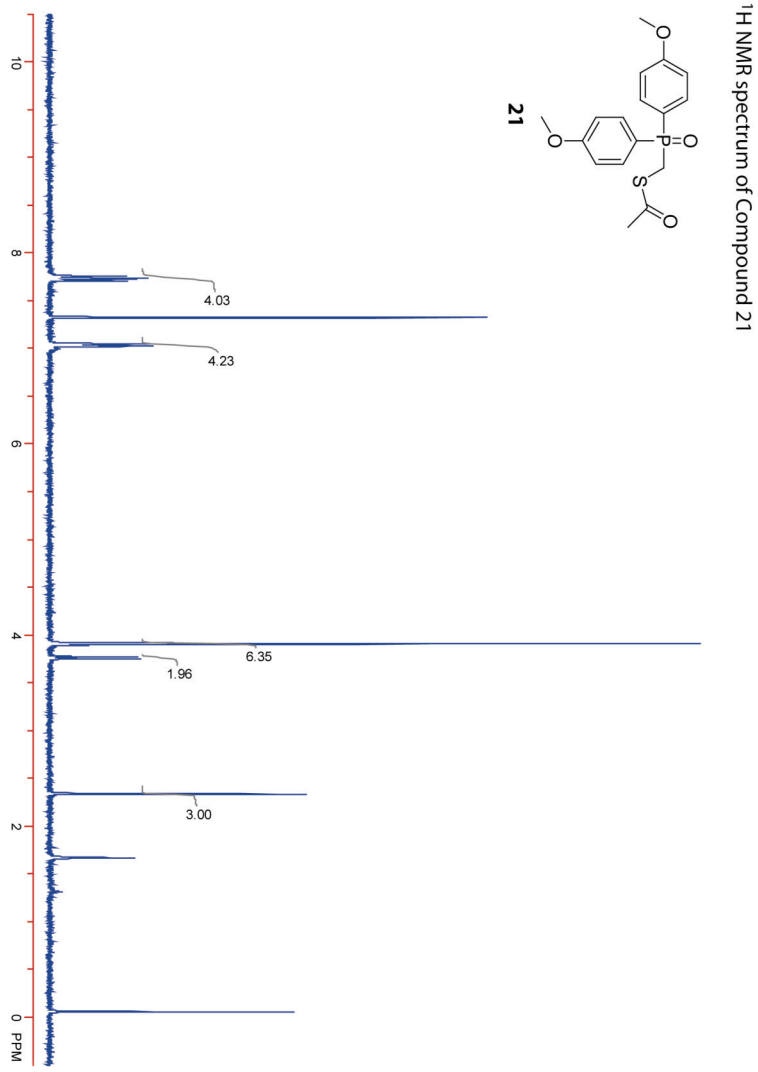


400 MHz ^{1}H NMR spectrum of Compound 21



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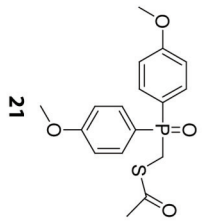
125 MHz ^{13}C NMR spectrum of Compound 21



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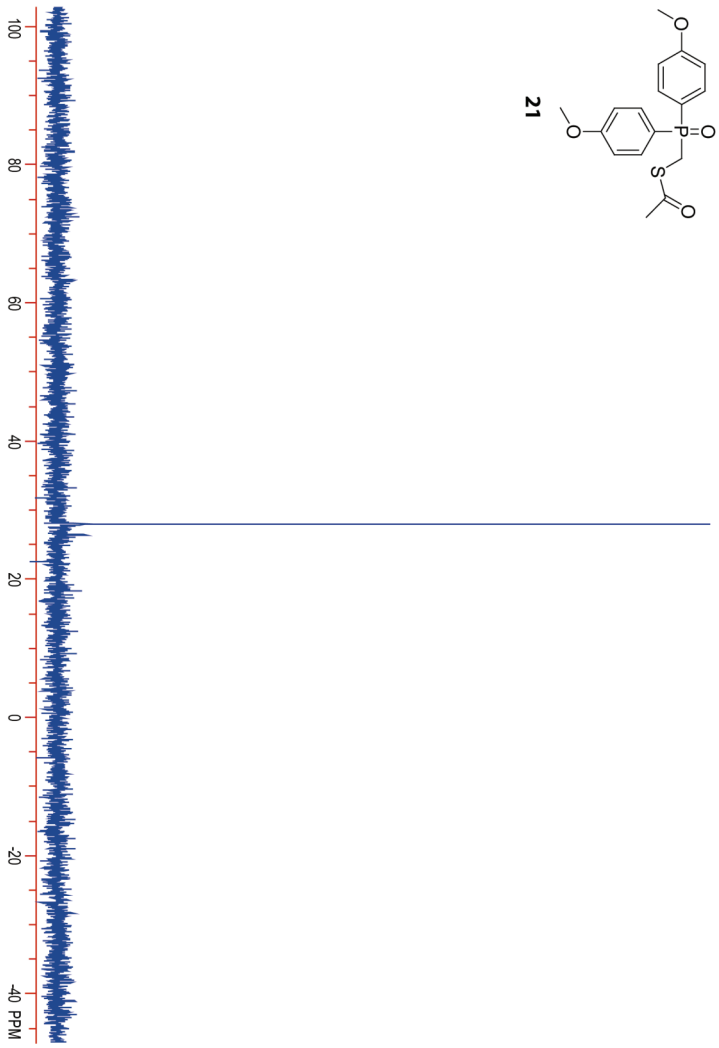
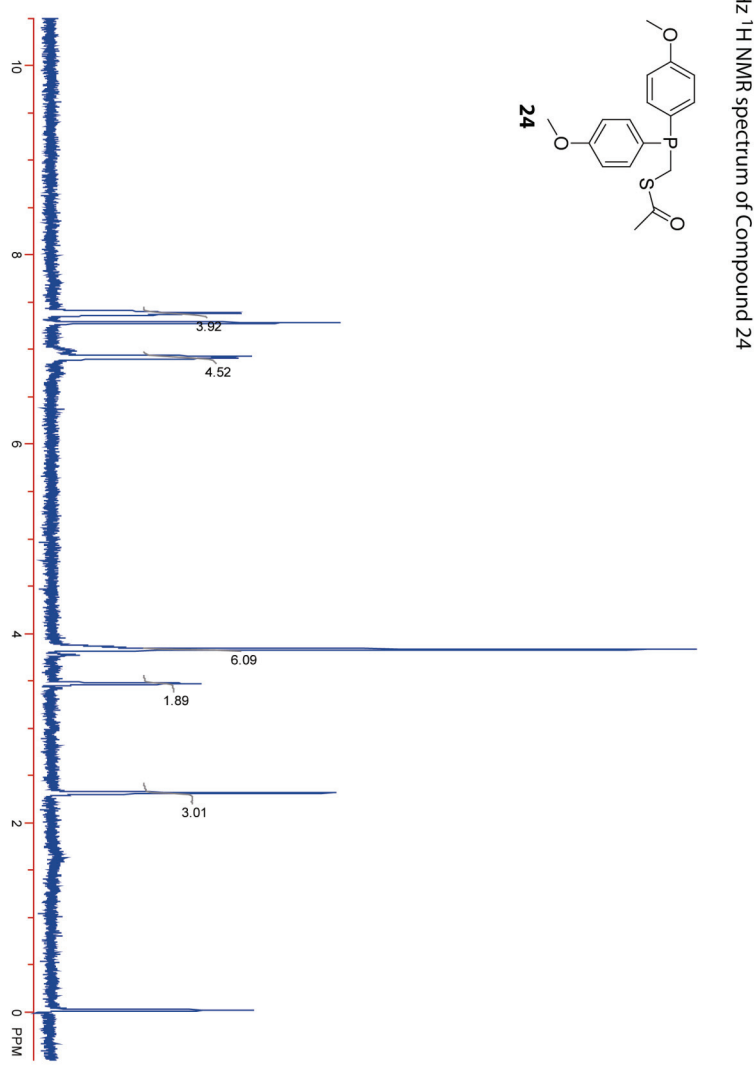
161 MHz ^{31}P NMR spectrum of Compound 21

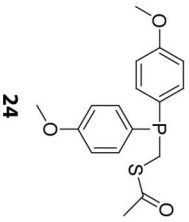


21

400 MHz ^{1}H NMR spectrum of Compound 24

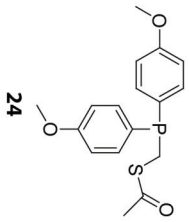


125 MHz ^{13}C NMR spectrum of Compound 24



24

161 MHz ^{31}P NMR spectrum of Compound 24



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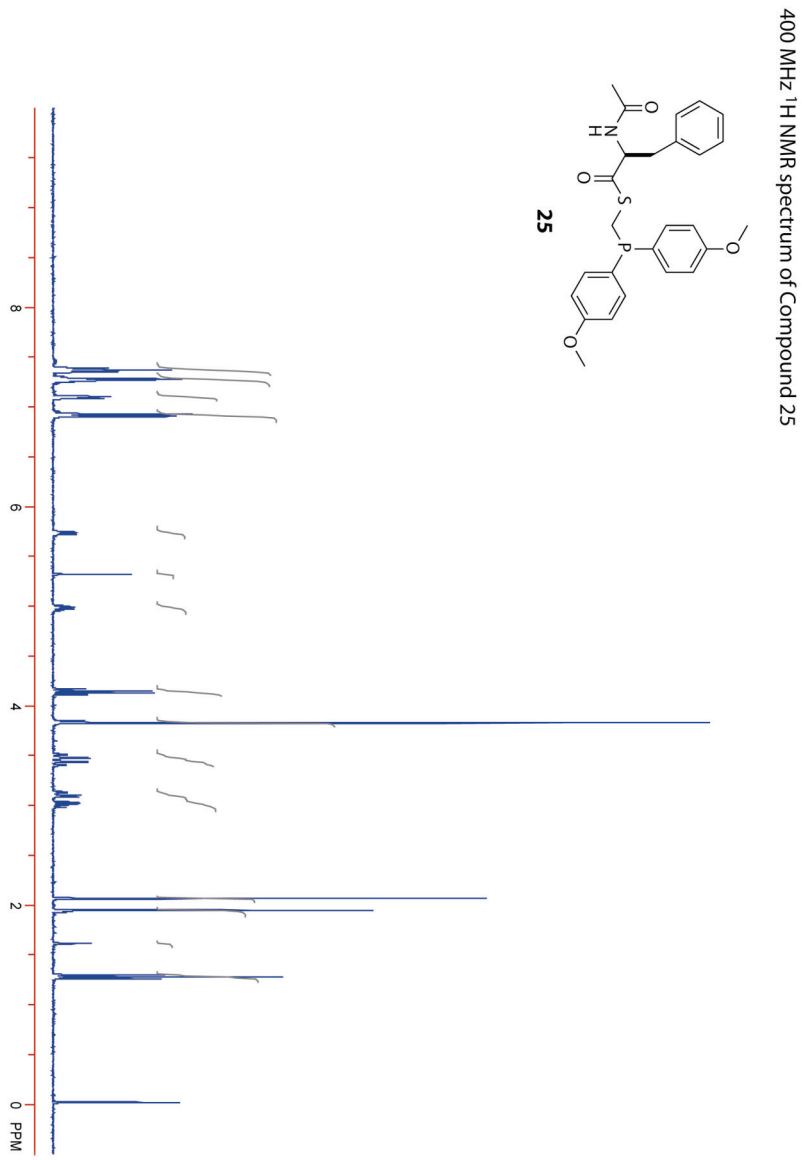
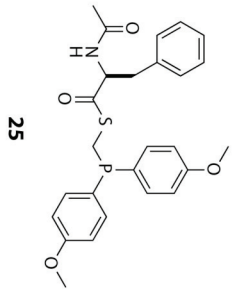
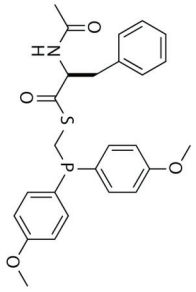

400 MHz ¹H NMR spectrum of Compound 25
25
8
6
4
2
0 PPM

125 MHz ^{13}C NMR spectrum of Compound 25



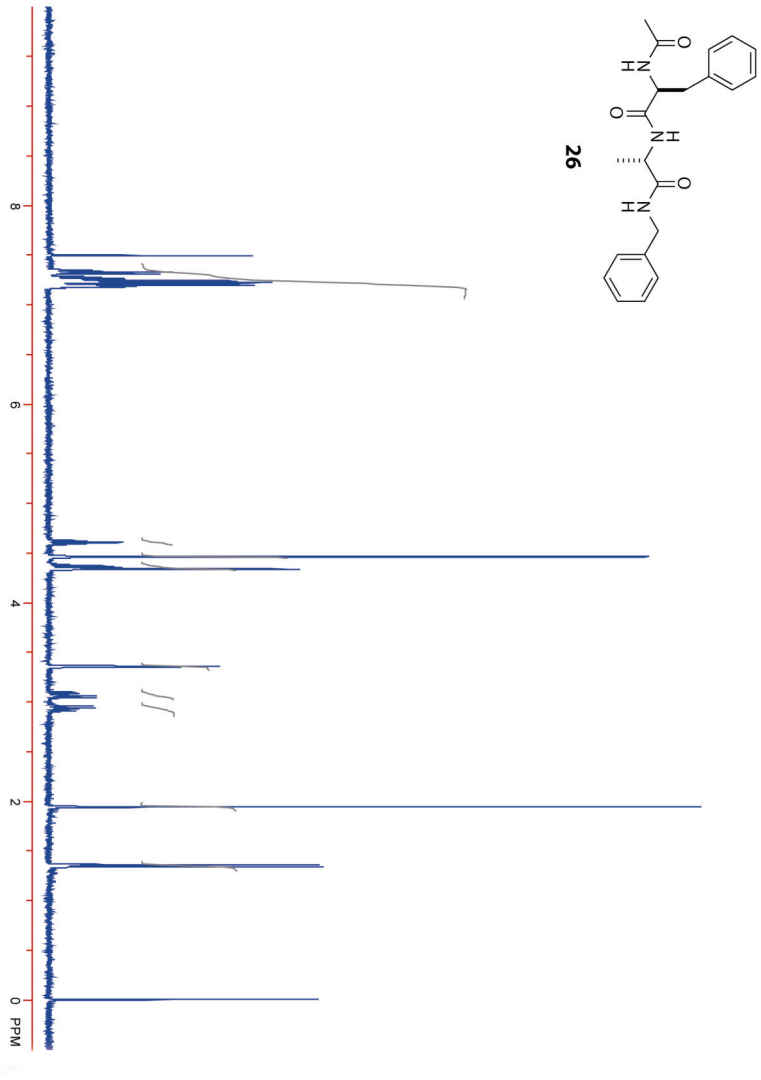
25

161 MHz ^{31}P NMR spectrum of Compound 25



25

400 MHz ^{1}H NMR spectrum of Compound 26



26

125 MHz ^{13}C NMR spectrum of Compound 26

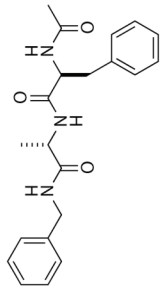


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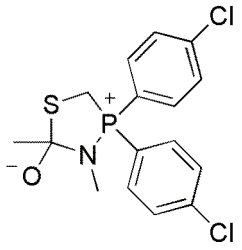
Table 1, Cl entry

Energy (Hartrees) and optimized geometry (B3LYP/6-31+G(d,p)):

$E = -695.1208559674$ $ZPVE = 0.235964$

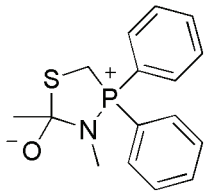


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.087465	1.897620	0.236664
2	1	0	0.763455	1.627702	1.059299
3	1	0	-0.908136	2.053239	0.674989
4	15	0	-0.014978	0.481974	-1.037368
5	16	0	0.652079	3.279920	-0.745653
6	6	0	0.930322	4.658624	0.425765
7	6	0	0.686879	4.398047	1.891132
8	1	0	-0.330365	4.019619	2.061876
9	1	0	1.393182	3.648920	2.275219
10	1	0	0.807687	5.304554	2.500347
11	8	0	1.301472	5.742801	0.033235
12	6	0	-1.585797	-0.321909	-0.468370
13	6	0	-2.747954	0.361930	-0.812976
14	6	0	-1.669177	-1.551367	0.172937
15	6	0	-3.995169	-0.175209	-0.514242
16	1	0	-2.676151	1.329083	-1.326692
17	6	0	-2.910070	-2.103373	0.475414
18	1	0	-0.750994	-2.089760	0.444276
19	6	0	-4.066875	-1.408851	0.130129
20	1	0	-4.914044	0.357424	-0.782563
21	1	0	-2.982797	-3.073546	0.978812
22	6	0	1.318758	-0.659998	-0.443357
23	6	0	2.111169	-1.153375	-1.474149
24	6	0	1.587007	-1.017915	0.872933
25	6	0	3.173376	-2.008302	-1.197002
26	1	0	1.893962	-0.858976	-2.509022
27	6	0	2.646496	-1.870694	1.165360
28	1	0	0.965953	-0.631536	1.690477
29	6	0	3.433422	-2.361350	0.125301
30	1	0	3.802686	-2.400379	-2.003481
31	1	0	2.865786	-2.157453	2.199600
32	17	0	4.716987	-3.394384	0.473080
33	17	0	-5.572851	-2.069316	0.494492

Table 1, H entry

Energy (Hartrees) and optimized geometry (B3LYP/6-31+G(d,p)):

$E = -586.9660504650$ $ZPVE = 0.254291$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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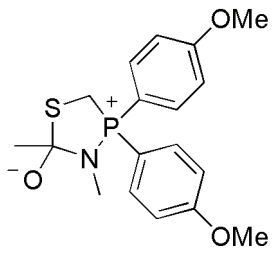
2	1	0	0.000000	0.000000	1.099057
3	1	0	1.050846	0.000000	-0.320794
4	15	0	-0.875090	1.580726	-0.611304
5	16	0	-0.979824	-1.317847	-0.704786
6	6	0	-0.098723	-2.871334	-0.309881
7	6	0	1.196692	-2.773406	0.456627
8	1	0	1.960185	-2.250699	-0.136195
9	1	0	1.060240	-2.217465	1.394381
10	1	0	1.602632	-3.761190	0.715284
11	8	0	-0.542198	-3.944355	-0.656656
12	6	0	0.353147	2.200615	-1.852595
13	6	0	-0.174811	2.380910	-3.125341
14	6	0	1.692526	2.478115	-1.611298
15	6	0	0.636360	2.840509	-4.159290
16	1	0	-1.232701	2.154471	-3.308017
17	6	0	2.506528	2.938282	-2.641952
18	1	0	2.109152	2.342342	-0.605327
19	6	0	1.977607	3.119168	-3.916440
20	1	0	0.219469	2.980931	-5.161937
21	1	0	3.561480	3.159219	-2.450038
22	1	0	2.617599	3.480992	-4.727905
23	6	0	-0.604607	2.724457	0.823624
24	6	0	-1.636570	3.638396	1.001596
25	6	0	0.476694	2.724019	1.695813
26	6	0	-1.588378	4.554240	2.048705
27	1	0	-2.489438	3.629416	0.311472
28	6	0	0.527908	3.636429	2.745613
29	1	0	1.295076	2.005699	1.561890
30	6	0	-0.504700	4.552405	2.921307
31	1	0	-2.402241	5.273694	2.185997
32	1	0	1.380740	3.634250	3.432165
33	1	0	-0.464343	5.270930	3.746574

Table 1, OMe entry

Energy (Hartrees) and optimized geometry (B3LYP/6-31+G(d,p)):

$E = -710.3092017285$ $ZPVE = 0.289409$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
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3	1	0	1.050033	0.000000	-0.324081
4	15	0	-0.838331	1.582446	-0.666642
5	16	0	-0.965191	-1.317421	-0.725521
6	6	0	-0.293159	-2.874031	-0.041014
7	6	0	0.848235	-2.779129	0.940626
8	1	0	1.694521	-2.226749	0.509441
9	1	0	0.534107	-2.253311	1.852944
10	1	0	1.220237	-3.767614	1.243661
11	8	0	-0.752206	-3.948062	-0.364899
12	6	0	0.669532	2.615682	-0.950232
13	6	0	1.406436	2.280533	-2.081831
14	6	0	1.047618	3.710225	-0.183468
15	6	0	2.519336	3.024724	-2.448594
16	1	0	1.100016	1.419821	-2.689762
17	6	0	2.155679	4.470866	-0.534594
18	1	0	0.464952	3.975713	0.709267
19	6	0	2.903636	4.127597	-1.670357
20	1	0	3.088314	2.745309	-3.343250
21	1	0	2.437154	5.333025	0.081571
22	6	0	-1.594184	2.288450	0.865402
23	6	0	-2.891515	2.750551	0.672417
24	6	0	-1.014975	2.368009	2.126140
25	6	0	-3.613985	3.293701	1.726695
26	1	0	-3.343207	2.677754	-0.325257
27	6	0	-1.720798	2.905544	3.194861
28	1	0	0.007961	2.005698	2.287490
29	6	0	-3.027642	3.377523	2.998731
30	1	0	-4.636003	3.652551	1.556295
31	1	0	-1.249420	2.959643	4.183326
32	7	0	4.104616	4.835042	-1.976905
33	1	0	4.319942	4.795675	-2.948179
34	1	0	4.073850	5.775417	-1.651285
35	7	0	-3.718716	4.028739	4.063216
36	1	0	-4.706724	3.967446	3.957389
37	1	0	-3.427958	3.694218	4.954648

Table 2, H_2O entry

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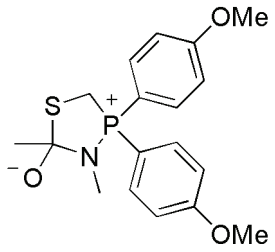
$E = -780.6118320298$ $ZPVE = 0.297677$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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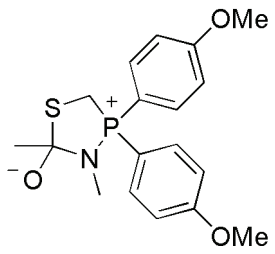
2	6	0	0.000000	0.000000	1.577141
3	16	0	2.215100	0.000000	1.772724
4	6	0	2.598875	-1.100987	0.422063
5	8	0	-0.530826	-1.007783	2.052438
6	6	0	3.024196	2.291200	-3.737407
7	6	0	3.002645	2.528966	-2.367099
8	6	0	2.474782	1.573851	-1.503331
9	6	0	1.963909	0.378442	-2.007599
10	6	0	1.990809	0.144343	-3.378997
11	6	0	2.519710	1.096285	-4.243379
12	6	0	-1.329047	-0.091959	-0.617294
13	6	0	-0.220186	1.402598	2.126633
14	1	0	3.605171	-0.905066	0.020425
15	1	0	2.595407	-2.170722	0.706857
16	1	0	3.439116	3.042054	-4.418595
17	1	0	3.401472	3.466258	-1.963809
18	1	0	2.464421	1.747409	-0.410403
19	1	0	1.592880	-0.796874	-3.782128
20	1	0	2.538618	0.905416	-5.321602
21	1	0	-1.241042	-0.170710	-1.714729
22	1	0	-1.914119	-0.950103	-0.253286
23	1	0	-1.878301	0.826778	-0.370917
24	1	0	-0.049832	1.414639	3.211297
25	1	0	0.449791	2.145171	1.673688
26	1	0	-1.254357	1.727516	1.946610
27	15	0	1.322679	-0.777682	-0.813530
28	6	0	0.846679	-2.294516	-1.645043
29	6	0	1.464330	-3.485688	-1.272231
30	6	0	-0.138669	-2.322545	-2.629407
31	6	0	1.124328	-4.684428	-1.890260
32	1	0	2.215642	-3.471994	-0.463898
33	6	0	-0.482760	-3.516870	-3.253015
34	1	0	-0.670222	-1.391118	-2.888299
35	6	0	0.153401	-4.699450	-2.886854
36	1	0	1.615917	-5.615142	-1.586575
37	1	0	-1.259043	-3.527036	-4.025706
38	1	0	-0.116466	-5.641702	-3.376230

Table 2, THF entry

Energy (Hartrees) and optimized geometry (B3LYP/6-31+G(d,p), scrf=(cpcm,solvent=THF)):

$E = -$ 780.6118320298 $ZPVE =$ 0.297677



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.577141
3	16	0	2.215100	0.000000	1.772724
4	6	0	2.598875	-1.100987	0.422063
5	8	0	-0.530826	-1.007783	2.052438
6	6	0	3.024196	2.291200	-3.737407
7	6	0	3.002645	2.528966	-2.367099
8	6	0	2.474782	1.573851	-1.503331
9	6	0	1.963909	0.378442	-2.007599
10	6	0	1.990809	0.144343	-3.378997
11	6	0	2.519710	1.096285	-4.243379
12	6	0	-1.329047	-0.091959	-0.617294
13	6	0	-0.220186	1.402598	2.126633
14	1	0	3.605171	-0.905066	0.020425
15	1	0	2.595407	-2.170722	0.706857
16	1	0	3.439116	3.042054	-4.418595
17	1	0	3.401472	3.466258	-1.963809
18	1	0	2.464421	1.747409	-0.410403
19	1	0	1.592880	-0.796874	-3.782128
20	1	0	2.538618	0.905416	-5.321602
21	1	0	-1.241042	-0.170710	-1.714729
22	1	0	-1.914119	-0.950103	-0.253286
23	1	0	-1.878301	0.826778	-0.370917
24	1	0	-0.049832	1.414639	3.211297
25	1	0	0.449791	2.145171	1.673688
26	1	0	-1.254357	1.727516	1.946610
27	15	0	1.322679	-0.777682	-0.813530
28	6	0	0.846679	-2.294516	-1.645043
29	6	0	1.464330	-3.485688	-1.272231
30	6	0	-0.138669	-2.322545	-2.629407
31	6	0	1.124328	-4.684428	-1.890260
32	1	0	2.215642	-3.471994	-0.463898
33	6	0	-0.482760	-3.516870	-3.253015
34	1	0	-0.670222	-1.391118	-2.888299
35	6	0	0.153401	-4.699450	-2.886854
36	1	0	1.615917	-5.615142	-1.586575
37	1	0	-1.259043	-3.527036	-4.025706
38	1	0	-0.116466	-5.641702	-3.376230