

Support Information for jo050944c

Synthesis of Methoxy-Substituted Phenols by Peracid Oxidation of the Aromatic Ring.

Hans-René Bjørsvik,* Giovanni Occhipinti, Cristian Gambarotti,
Leonardo Cerasino, and Vidar R. Jensen
Department of Chemistry, University of Bergen, Allégaten 41, N-5007 Bergen, Norway

Table of content

Experimental	S1
General Methods	S1
Synthesis of 1-(2,4-Dimethoxy-3-methylphenyl)-ethanone (2).	S1
Compound data	S1
¹H and ¹³C spectra	
¹ H NMR spectrum of 5 2,4-Dimethoxy-3-methylphenol	S3
¹³ C NMR spectrum of 5 2,4-Dimethoxy-3-methylphenol	S3
¹ H NMR spectrum of 8d Acetic acid 4,5-dimethoxy-3,6-dioxocyclohexa-1,4-dienyl ester	S4
¹³ C NMR spectrum of 8d Acetic acid 4,5-dimethoxy-3,6-dioxocyclohexa-1,4-dienyl ester	S4
¹ H NMR spectrum of 9b Acetic acid 3-hydroxy-2,6-dimethoxyphenyl ester	S5
¹³ C NMR spectrum of 9b Acetic acid 3-hydroxy-2,6-dimethoxyphenyl ester	S5
Cartesian coordinates of geometry optimized species.	S6
Structure of protonated ethene epoxide (Figure 2a).	S6
Transition state for epoxidation of ethene by ethaneperoxoic acid (Figure 2b).	S6
Second order saddle point structure for benzene and s-cis ethaneperoxoic acid. (Figure 3a)	S6
Saddle point (transition state TS) structure for benzene and s-cis ethaneperoxoic acid. (Figure 3b)	S7
TS structure for 2,6-dimethoxytoluene and s-cis ethaneperoxoic acid. (Figure 3c)	S7
TS structure for 2,6-dimethoxyacetophenone and s-cis ethaneperoxoic acid. (Figure 3d)	S8

Experimental

General Methods.

GLC analyses were performed on a capillary gas chromatograph equipped with fused silica column (L 25 m, 0.20 mm i.d., 0.33 μm film thickness) at a helium pressure of 200 kPa, split less /split injector and flame ionization detector. Mass spectra were acquired on a GC-MS instrument using a gas chromatograph equipped with fused silica column (L 30 m, 0.25 mm i.d., 0.25 μm film thickness) and He as carrier gas. ¹H-NMR spectra were recorded on NMR spectrometers operating at 200 MHz and 400 MHz. Chemical shifts were referenced to internal TMS. Starting materials and reagents were purchased commercially and used without further purification. Except reaction products **8d** and **9b**, were all of the reaction products known. The reaction products were analyzed by GC and GC-MS and by comparison with authentic samples. The products **5**, **8d**, and **9b** were in addition characterized with ¹H-NMR and ¹³C NMR. Silica gel 60 (0.040-0.0063 mm) was used for the flash chromatography. F-254 TLC plates were used in order to follow the progress of the reactions, the purity of substance and to identify the various fractions from the flash chromatography separation. The spots of substances on the thin-layer were visualized under UV light.

1-(2,4-Dimethoxy-3-methylphenyl)-ethanone 2.

1,3-dimethoxy-2-methylbenzene 1 (1.0 g, 6.57 mmol) was dissolved in nitroethane (5 mL). Acetyl chloride (0.5 mL, 0.55 g, 7 mmol) was then added followed by portion-wise addition of anhydrous aluminum chloride (1.0 g, 7.5 mmol) to keep the reaction temperature in the range 25-35 °C. The reaction mixture was then heated at a temperature of 45 °C for one hour. The reaction mixture was quenched by adding it to an ice water (90 g)-hydrochloric acid (10 mL, 37%) mixture followed by extraction with dichloromethane (2 × 50 mL). The organic layer was washed twice with dilute sodium hydroxide solution (5% sol, 50 mL) and with water (1 × 50 mL). The dichloromethane layer was dried over sodium sulfate, filtered and evaporated under vacuum to achieve a practically pure product with a yield of 96% (1.27 g).

Compound data.

2,4-Dimethoxy-3-methyl-phenol 5, [19676-67-6], C₉H₁₂O₃, MW 168.19, MS (m/z) 168 M⁺, 153, 125, 110, 107, 93, 82, 79, 65, 53. ¹H NMR (CDCl₃): 6.75 (d, 8.9Hz, 1H, CH), 6.53 (d, 8.9Hz, 1H, CH), 3.78 (s, 3H, CH₃), 3.77 (s, 3H, CH₃), 2.17 (s, 3H, CH₃).

1-(2-Hydroxy-3,5-dimethoxy-phenyl)-ethanone 6a, [17605-00-4], C₁₀H₁₂O₄, MW 196.20, MS (m/z) 196 M⁺, 181, 163, 153, 135, 125, 95, 79, 69.

1-(4-Hydroxy-3,5-dimethoxy-phenyl)-ethanone 6b, [2478-38-8], C₁₀H₁₂O₄, MW 196.20, MS (m/z) 196 M⁺, 181, 167, 153, 138, 123, 108, 67.

* To whom correspondence should be sent. Phone: +47 55 58 54 52, Fax: +47 55 58 94 90, e-mail: hans.bjorsvik@kj.uib.no

Acetic acid 3,4-dimethoxy-phenyl ester 7a, [7203-46-5], C₁₀H₁₂O₄, MW 196.20, MS (m/z) 196 M⁺, 154, 139, 111, 93, 79, 69.

Acetic acid 3,4,5-trimethoxy-phenyl ester 8a, [17742-46-0], C₁₁H₁₄O₅, MW 226.23, MS (m/z) 226 M⁺, 184, 169, 141, 126, 109, 69.

1-(2-Hydroxy-3,4,5-trimethoxy-phenyl)-ethanone 8b, [30225-96-8], C₁₁H₁₄O₅, MW 226.23, MS (m/z) 226 M⁺, 211, 193, 183, 168, 165, 153, 150, 140, 98, 82, 69.

2,6-Dimethoxy-[1,4]benzoquinone 8c, [530-55-2], C₈H₈O₄, MW 168.15, MS (m/z) 168 M⁺, 138, 125, 97, 80, 69, 59, 53.

Acetic acid 4,5-dimethoxy-3,6-dioxocyclohexa-1,4-dienyl ester 8d, [Previously not registered in CAS], C₁₀H₁₀O₆, MW 226.18, MS (m/z) 226 M⁺, 184, 169, 141, 113, 85, 69, 43; ¹H NMR (400 MHz, CDCl₃) δ 2.35 (s, 3H), 3.82 (s, 3H), 4.06 (s, 3H), 5.84 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 20.4, 56.7, 60.5, 105.3, 135.1, 146.7, 157.4, 167.9, 177.8, 180.3.

3,4,5-Trimethoxybenzoic acid methyl ester 8e, [1916-07-0], C₁₁H₁₄O₅, MW 226.23, MS (m/z) 226 M⁺, 211, 195, 183, 155, 137, 125, 109, 93, 77.

1-(3-Hydroxy-2,6-dimethoxy-phenyl)-ethanone 9a, [56358-74-8], C₁₀H₁₂O₄, MW 196.20, MS (m/z) 196 M⁺, 181, 166, 151, 135, 123, 95, 79, 69.

Acetic acid 3-hydroxy-2,6-dimethoxyphenyl ester 9b, [Previously not registered in CAS], C₁₀H₁₂O₅, MW 212.20, MS (m/z) 212 M⁺, 170, 155, 126, 109, 95, 83, 69; ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 6.62 (d, *J* = 9.1 Hz, 1H), 6.78 (d, *J* = 9.1 Hz, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 20.5, 56.5, 61.3, 107.4, 111.6, 132.9, 139.9, 140.0, 145.7, 168.4

Acetic acid 2,6-dimethoxy-phenyl ester 9c, [1916-07-0], C₁₀H₁₂O₄, MW 196.20, MS (m/z) 196 M⁺, 154, 139, 111, 93, 65.

Acetic acid 3-methoxyphenyl ester 10a, [5451-83-2], C₉H₁₀O₃, MW 166.18, MS (m/z) 166 M⁺, 124, 94, 81, 66.

1-(2-Hydroxy-3-methoxyphenyl)-ethanone 10b, [703-98-0], C₉H₁₀O₃, MW 166.18, MS (m/z) 166 M⁺, 151, 136, 133, 123, 121, 108, 105, 93, 77.

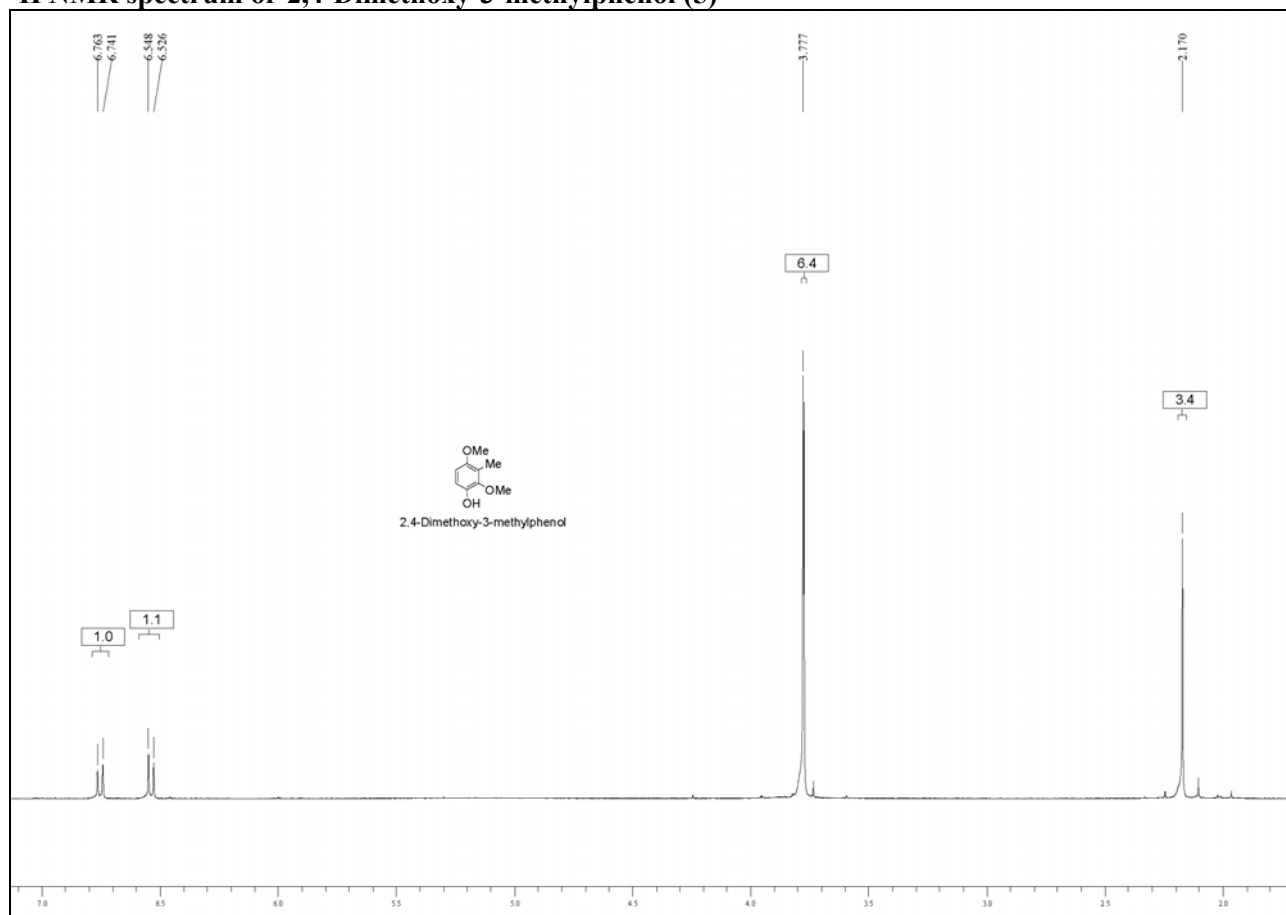
1-(2-Hydroxy-5-methoxyphenyl)-ethanone 10c, [705-15-7], C₉H₁₀O₃, MW 166.18, MS (m/z) 166 M⁺, 151, 135, 133, 123, 108, 105, 95, 77.

Acetic acid 4-methoxy-phenyl ester 11a, [1200-06-2], C₉H₁₀O₃, MW 166.18, MS (m/z) 166 M⁺, 124, 109, 81.

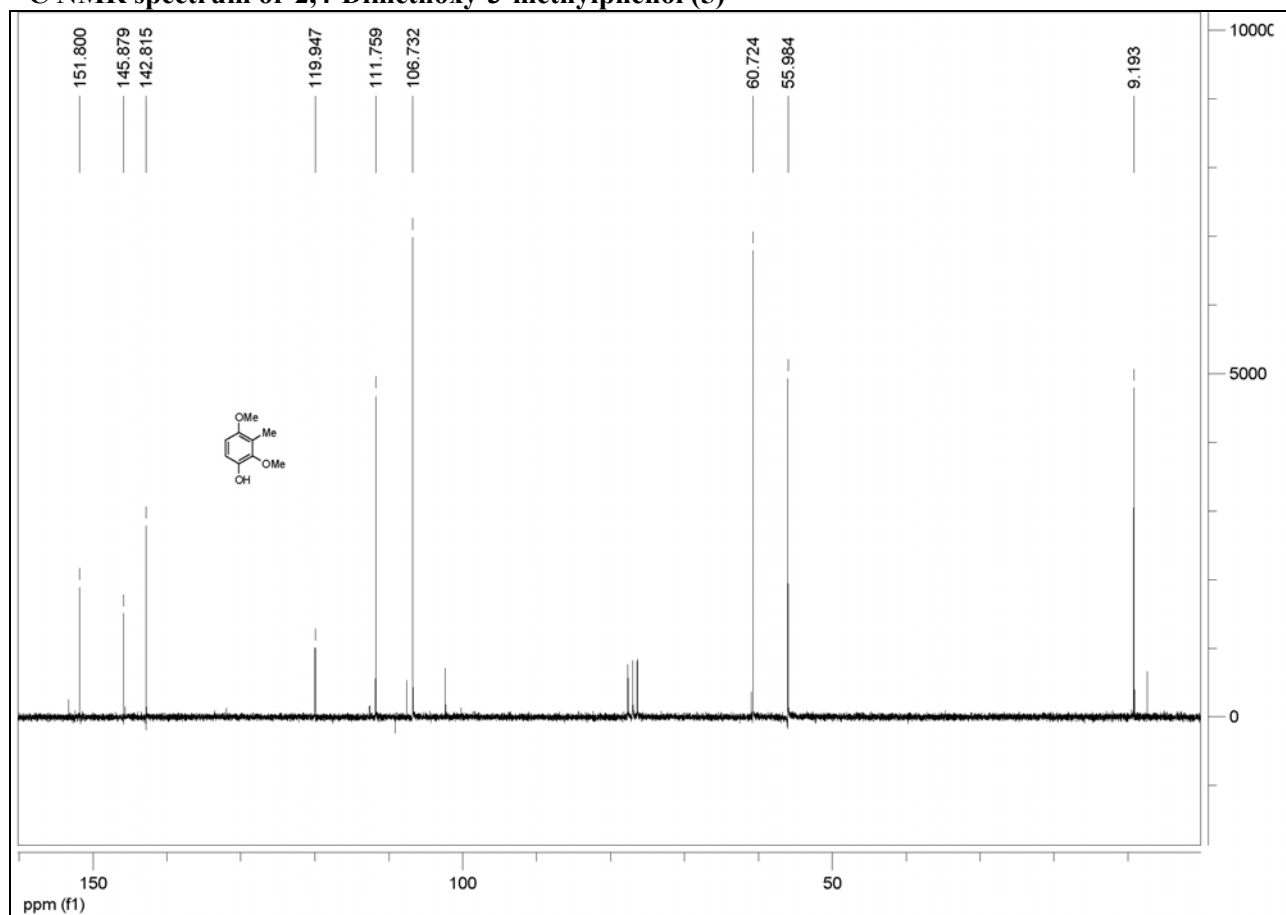
Acetic acid 2,5-dimethoxy-phenyl ester 12a, [27257-06-3], C₁₀H₁₂O₄, MW 196.20, MS (m/z) 196 M⁺, 154, 139, 111, 69.

2,5-Dimethoxy-[1,4]benzoquinone 12b, [3117-03-1], C₈H₈O₄, MW 168.15, MS (m/z) 168 M⁺, 153, 139, 95, 69, 59, 53.

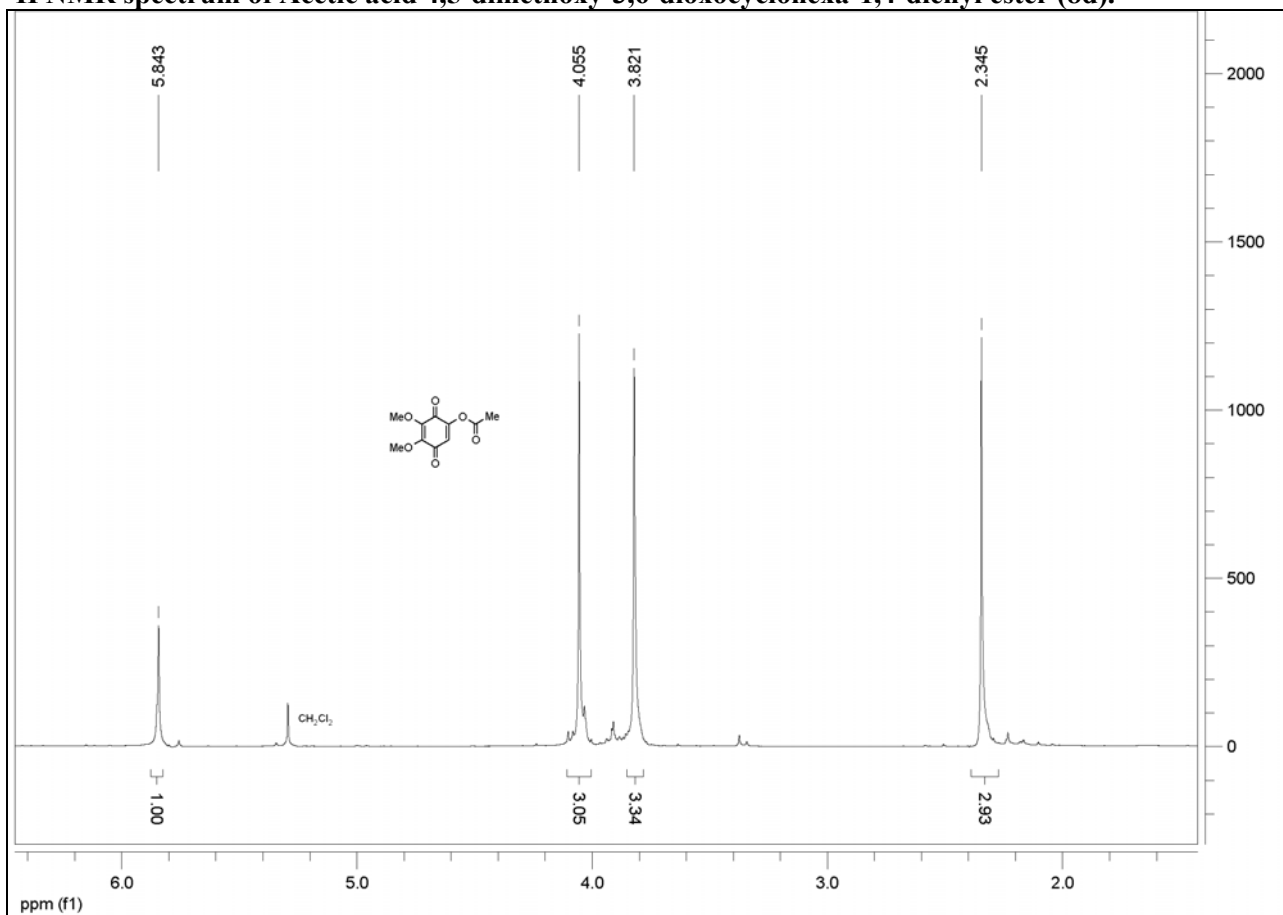
¹H NMR spectrum of 2,4-Dimethoxy-3-methylphenol (5)



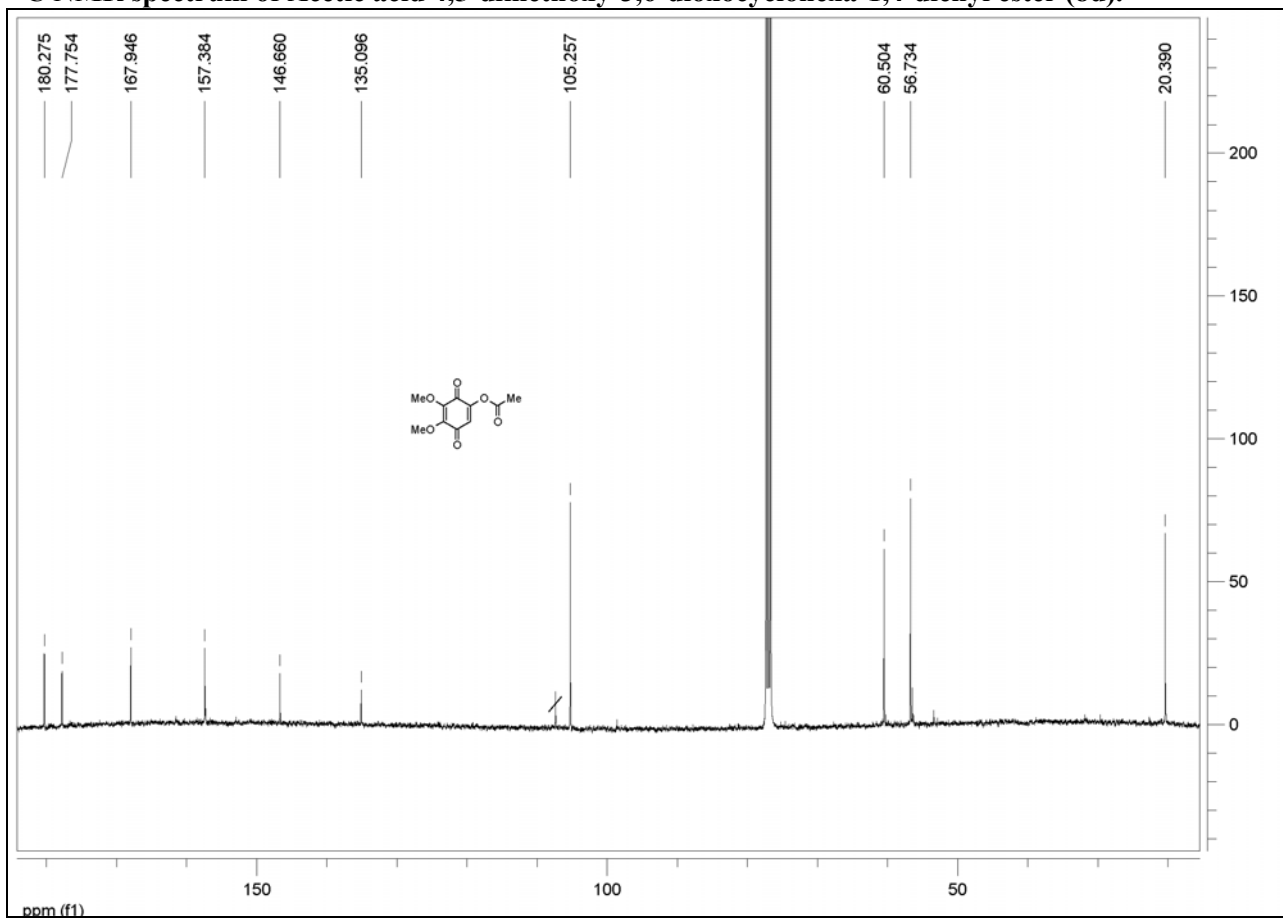
¹³C NMR spectrum of 2,4-Dimethoxy-3-methylphenol (5)



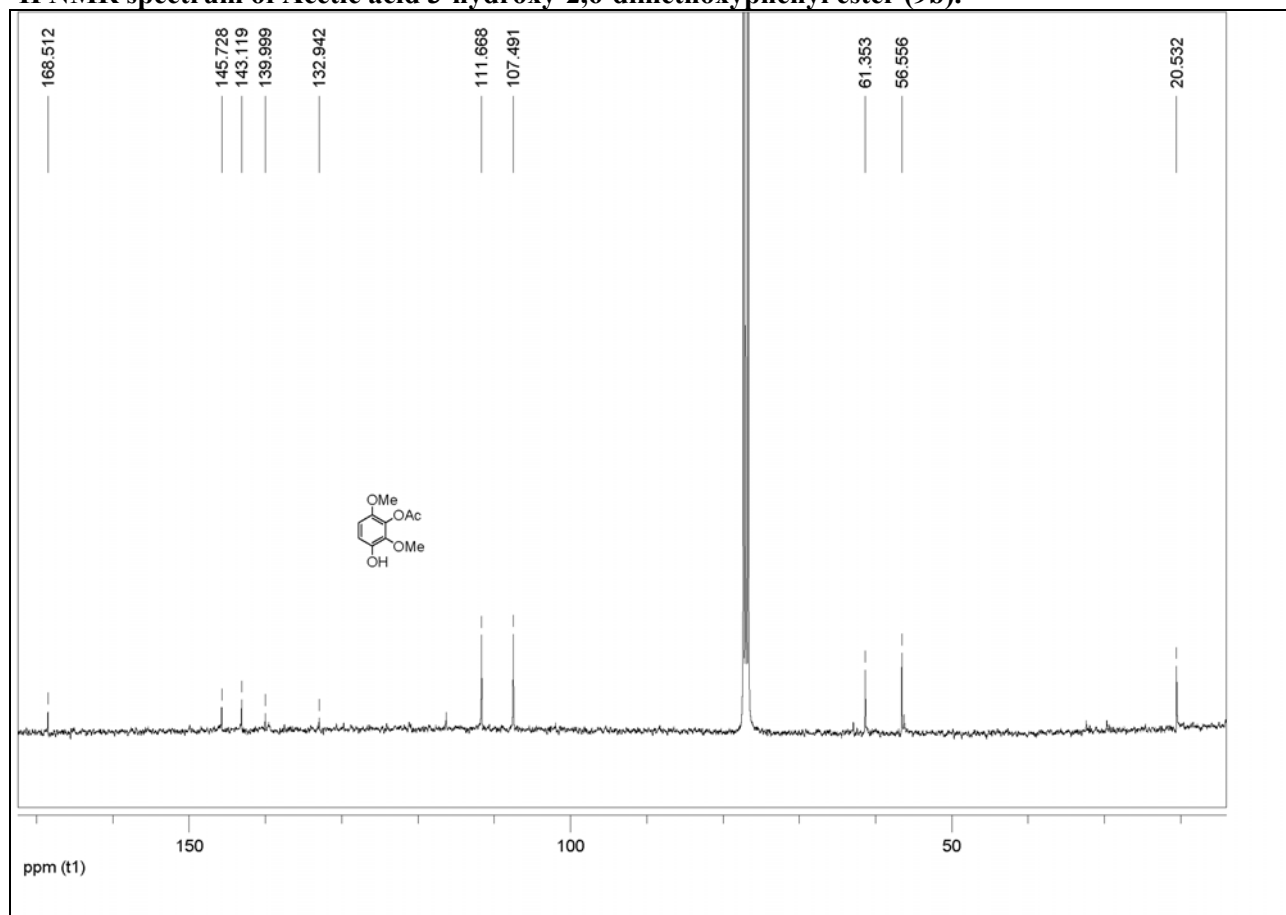
¹H NMR spectrum of Acetic acid 4,5-dimethoxy-3,6-dioxocyclohexa-1,4-dienyl ester (8d).



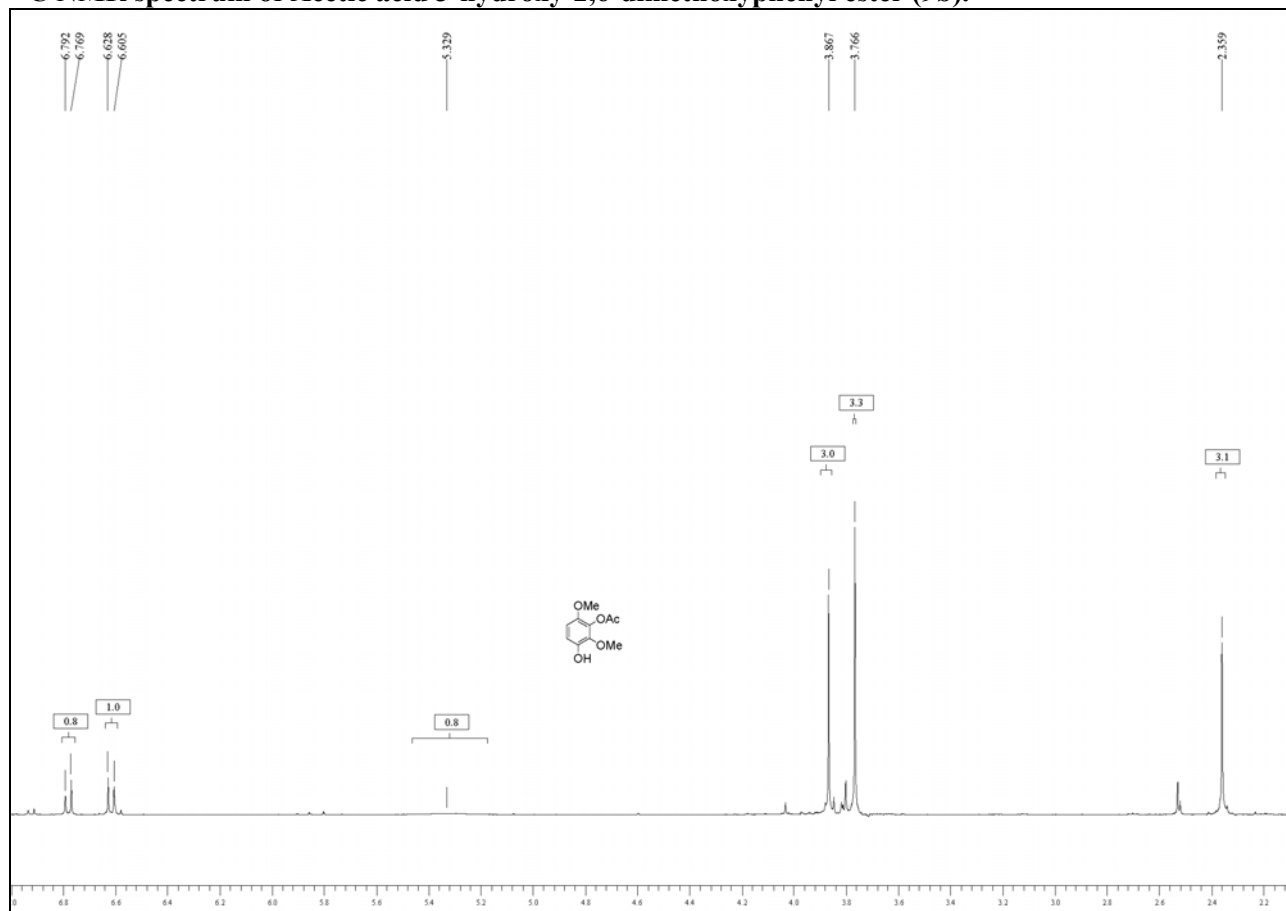
¹³C NMR spectrum of Acetic acid 4,5-dimethoxy-3,6-dioxocyclohexa-1,4-dienyl ester (8d).



¹H NMR spectrum of Acetic acid 3-hydroxy-2,6-dimethoxyphenyl ester (9b).



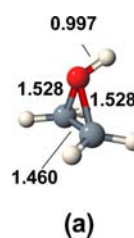
¹³C NMR spectrum of Acetic acid 3-hydroxy-2,6-dimethoxyphenyl ester (9b).



Cartesian coordinates of geometry optimized species.

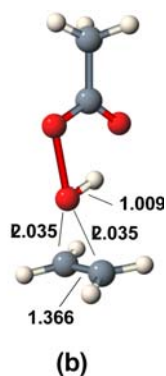
Structure of protonated ethene epoxide (Figure 2a).

O	0.034187	0.864478	0.000000
C	0.034187	-0.478175	0.730156
H	-0.886527	-0.659636	1.272610
H	0.964329	-0.580163	1.274862
C	0.034187	-0.478175	-0.730156
H	-0.886527	-0.659636	-1.272610
H	0.964329	-0.580163	-1.274862
H	-0.839337	1.301878	0.000000



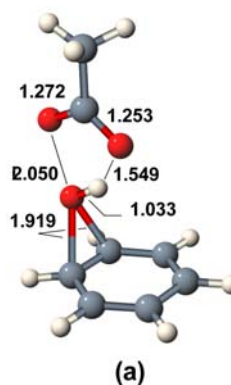
Transition state for epoxidation of ethene by etheneperoxoic acid (Figure 2b).

C	-1.506228	0.082365	-0.004433
H	-3.390018	0.396113	0.940494
H	-3.346705	-1.062127	-0.085142
O	-0.939702	1.187672	-0.002298
C	-3.018317	-0.028240	0.004975
H	-3.419139	0.568220	-0.816687
O	0.925980	-0.508378	-0.002489
H	0.505530	0.409250	-0.001470
O	-0.869697	-1.038989	-0.007072
C	2.733532	0.140756	-0.679743
C	2.729682	0.133189	0.686462
H	3.028983	-0.743357	1.244465
H	2.507676	1.028627	1.253913
H	2.513846	1.042234	-1.238485
H	3.035162	-0.729822	-1.245780



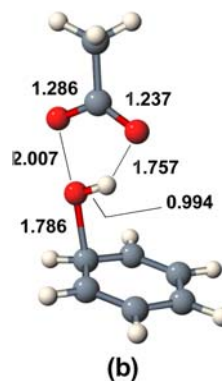
Second order saddle point structure for benzene and s-cis ethaneperoxoic acid. (Figure 3a)

O	-0.189191	1.109970	0.000098
C	1.591841	1.113623	0.714839
C	1.591739	1.113580	-0.714898
C	-2.428656	-0.178009	-0.000120
H	-4.035970	-1.279401	-0.880960
H	-4.568972	0.181680	-0.002212
O	-1.497640	-1.017111	-0.000068
C	-3.872556	-0.654931	0.000113
H	-4.036946	-1.274959	0.884161
H	-0.430955	0.105980	0.000062
O	-2.239117	1.080223	-0.000104
C	1.963507	-0.069574	-1.411959
H	1.488902	2.045311	-1.251456
H	1.489098	2.045389	1.251364
H	1.984686	-0.059136	2.494480
C	2.294473	-1.200911	-0.711076
H	2.571176	-2.105245	1.240161
H	2.571099	-2.105291	-1.240103
C	2.294518	-1.200883	0.711104
C	1.963636	-0.069517	1.411929
H	1.984461	-0.059258	-2.494502



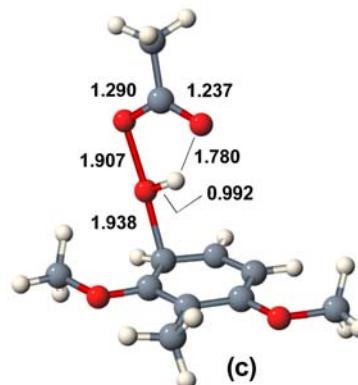
Saddle point (transition state TS) structure for benzene and s-cis ethaneperoxoic acid. (Figure 3b)

C	2.545220	-0.230497	-0.007070
H	4.204411	-1.244448	0.883589
H	4.680485	0.210794	-0.035280
O	1.652118	-1.096878	-0.012329
C	4.013854	-0.649402	-0.012273
H	4.189047	-1.283562	-0.883780
O	0.305987	1.095620	0.015052
H	0.469174	0.107514	0.002440
O	2.341132	1.030464	0.005184
C	-1.809116	0.635715	-1.213077
C	-1.431608	1.254404	0.028820
C	-1.793965	0.576384	1.243886
H	-1.395621	2.337017	0.054719
H	-1.583543	1.158215	-2.134691
H	-2.602605	-1.105234	-2.174430
C	-2.357549	-0.681862	1.209172
H	-3.087297	-2.271705	-0.046189
H	-2.575236	-1.209630	2.129722
C	-2.649866	-1.279774	-0.024929
C	-2.372927	-0.622699	-1.232237
H	-1.556966	1.053777	2.186888



TS structure for 2,6-dimethoxytoluene and s-cis ethaneperoxoic acid. (Figure 3c)

C	-3.231053	-1.095205	-0.322921
H	-4.429887	-1.804980	-1.942806
H	-5.379154	-0.989879	-0.672025
O	-2.186999	-1.756170	-0.372468
C	-4.539776	-1.655713	-0.866108
H	-4.718845	-2.630031	-0.407170
O	-1.555354	0.512038	0.740183
H	-1.337698	-0.389508	0.388276
O	-3.325093	0.094143	0.166592
C	0.686121	-0.149062	1.975247
C	0.213803	1.030527	1.337749
C	0.806619	1.403402	0.088188
H	-0.241045	1.793583	1.950588
H	0.279412	-0.406777	2.945254
H	1.897885	-1.895176	1.839267
C	1.728512	0.574375	-0.557353
O	2.991498	-1.372682	-0.582737
C	2.301939	0.911985	-1.908180
C	2.106698	-0.611010	0.094574
C	1.591244	-0.976248	1.361235
O	0.482327	2.545560	-0.540717
H	2.155734	0.082744	-2.604708
H	3.380082	1.087701	-1.844260
H	1.829491	1.802869	-2.315664
C	3.401629	-2.633675	-0.051131
C	-0.544648	3.395490	-0.006188
H	4.077412	-3.054363	-0.792904
H	2.545532	-3.299962	0.083989
H	3.933310	-2.508627	0.896442
H	-0.219617	3.849244	0.935053
H	-1.468155	2.834453	0.134475
H	-0.682020	4.176400	-0.751297



TS structure for 2,6-dimethoxyacetophenone and *s*-cis ethaneperoxoic acid. (Figure 3d)

C	3.460093	-0.835676	0.618824
H	4.518127	-1.145306	2.449570
H	5.559924	-0.556351	1.125256
O	2.419855	-1.492999	0.753727
C	4.726042	-1.208657	1.379100
H	4.978014	-2.245239	1.145777
O	1.853241	0.388434	-0.941682
H	1.637221	-0.414230	-0.397932
O	3.580457	0.194496	-0.146441
C	-0.204107	-0.635287	-2.253630
C	0.136183	0.659549	-1.770477
C	-0.588465	1.157357	-0.640685
H	0.587124	1.358906	-2.457858
H	0.300016	-0.996717	-3.141383
H	-1.293184	-2.440502	-1.950449
C	-1.501499	0.351353	0.036386
O	-2.603949	-1.673878	0.299928
C	-2.241391	0.876792	1.257909
C	-1.746465	-0.945742	-0.435347
C	-1.097519	-1.439843	-1.593529
O	-0.415589	2.393458	-0.150843
O	-3.400295	1.208803	1.173366
C	-1.453559	0.930416	2.542484
C	-2.933827	-3.008784	-0.092483
C	0.563065	3.269794	-0.736461
H	0.267143	3.549304	-1.751498
H	1.544358	2.795761	-0.734035
H	0.562837	4.155633	-0.105326
H	-3.638703	-3.361994	0.656741
H	-2.047079	-3.648134	-0.093506
H	-3.410516	-3.020358	-1.076166
H	-2.058681	1.369419	3.335420
H	-0.538130	1.509591	2.396614
H	-1.149545	-0.083920	2.821775

