Supplementary material

End-group-differentiating ozonolysis of furocoumarins

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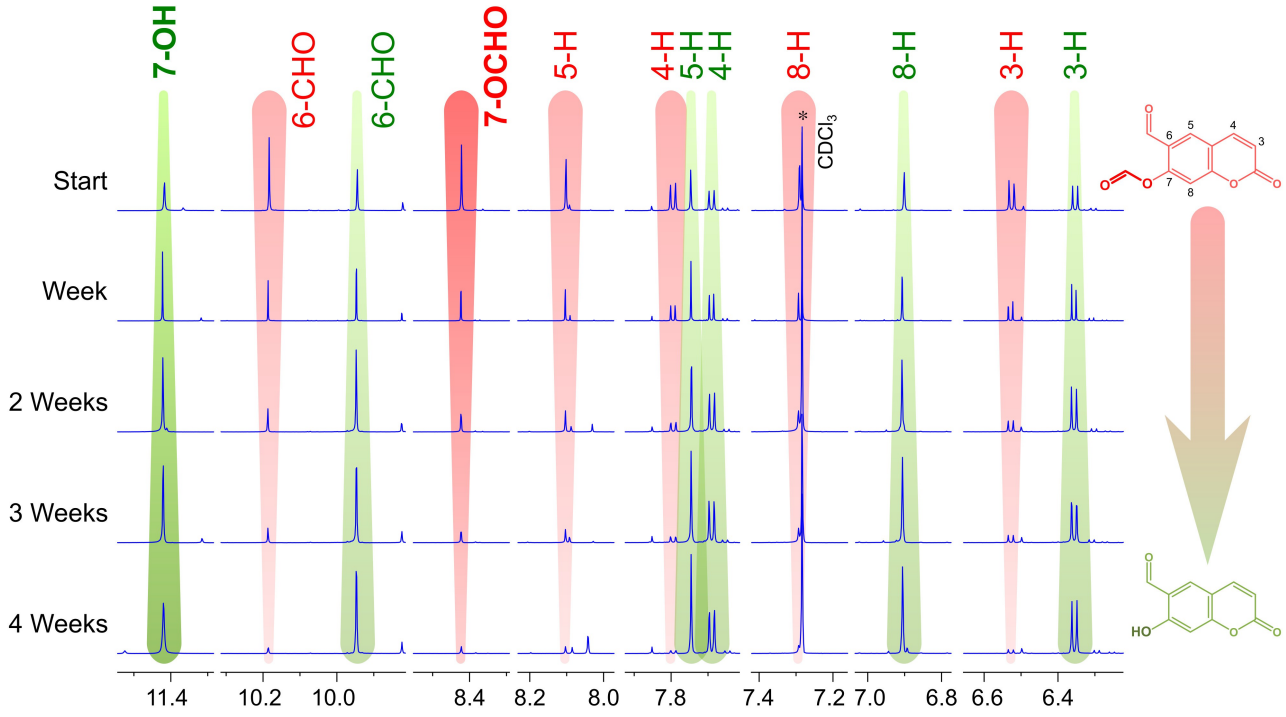
[c] *Orekhovich Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, ul. Pogodinskaya 10, Moscow 119121, Russia. Tel: +7-916-359-2656; E-mail: vic_zgoda@yahoo.com*

Contents

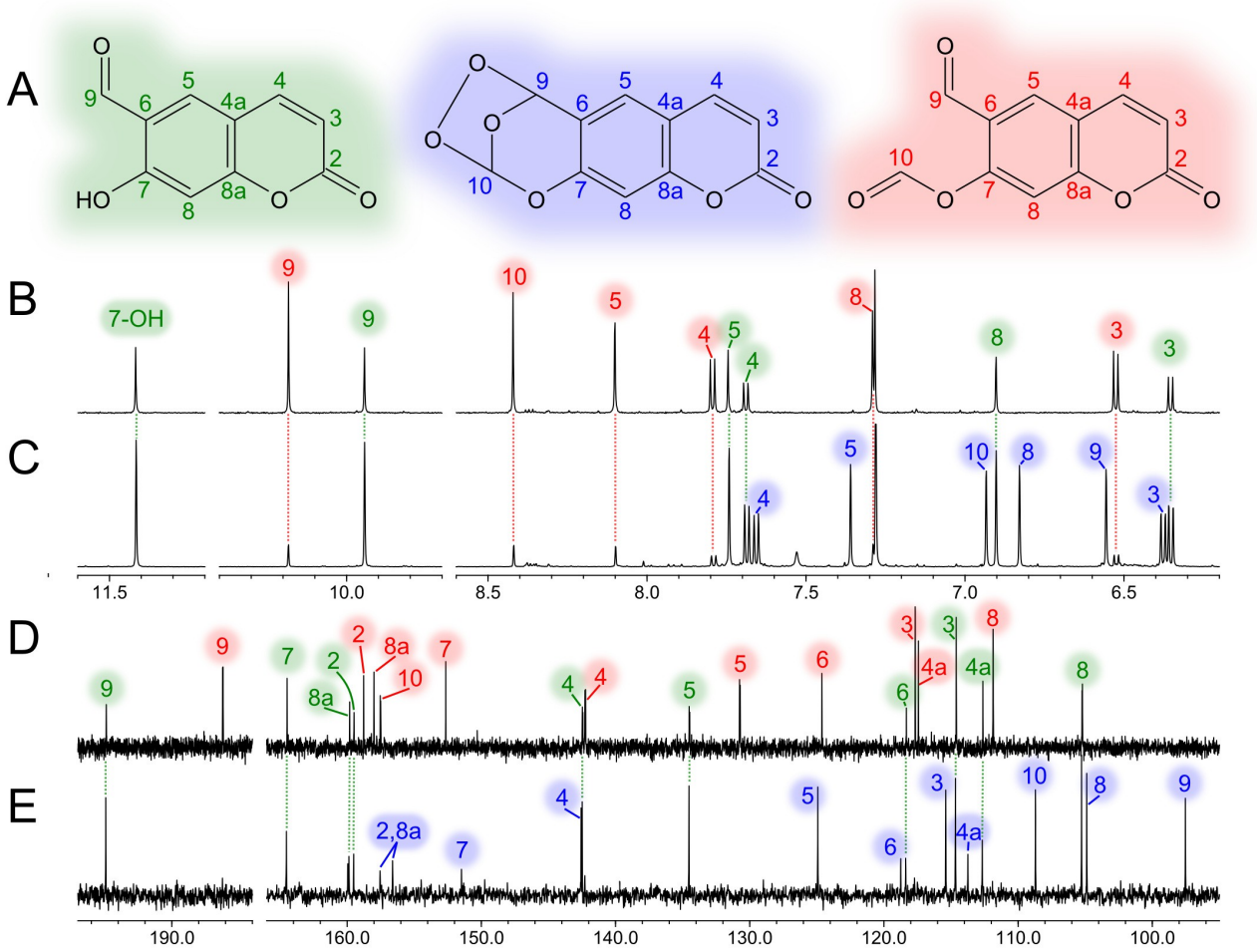
Figure S1 Hydrolysis of formate monitored by NMR



Products of furocoumarins' ozonolysis

Data are also summarized in table 1 in the main body of the article.

Figure S2. Psoralen ozonolysis products



A. Products of psoralen ozonolysis. Common, uncommon and trioxolane products are highlighted with red, green and blue color respectively.

B. 1H NMR spectrum of product mixture treated with Me_2S.

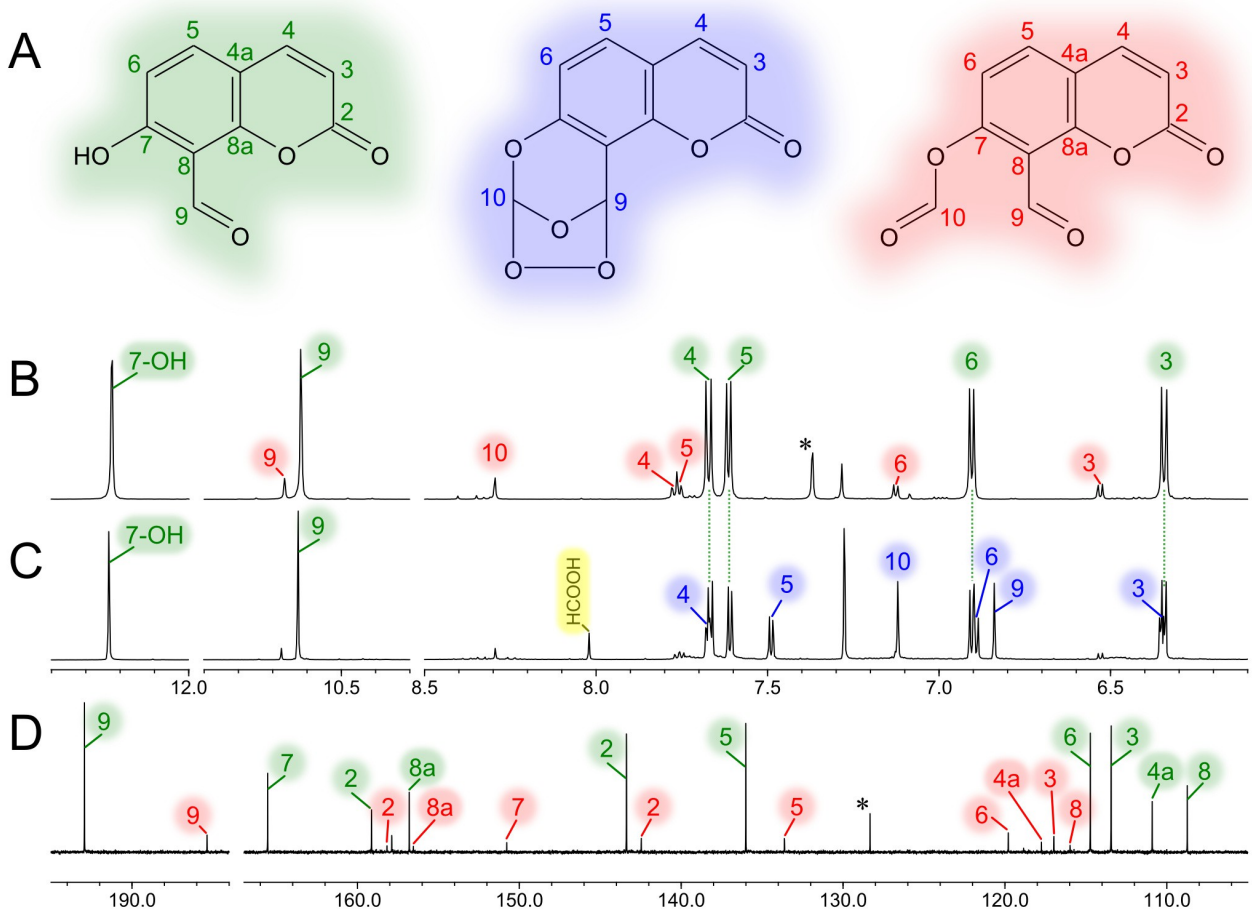
C. 1H NMR spectrum of product mixture processed without addition of Me_2S.

D. 13C NMR spectrum of product mixture treated with Me_2S

E. 13C NMR spectrum of product mixture processed without addition of Me_2S.

Mixtures non-treated with Me_2S contain trioxolane. Common and uncommon products are found among products regardless to Me_2S addition. Notably, formic acid is absent.

Figure S3. Angelicin ozonolysis products



A. Products of angelicin ozonolysis. Common, uncommon and trioxolane products are highlighted with red, green and blue color respectively.

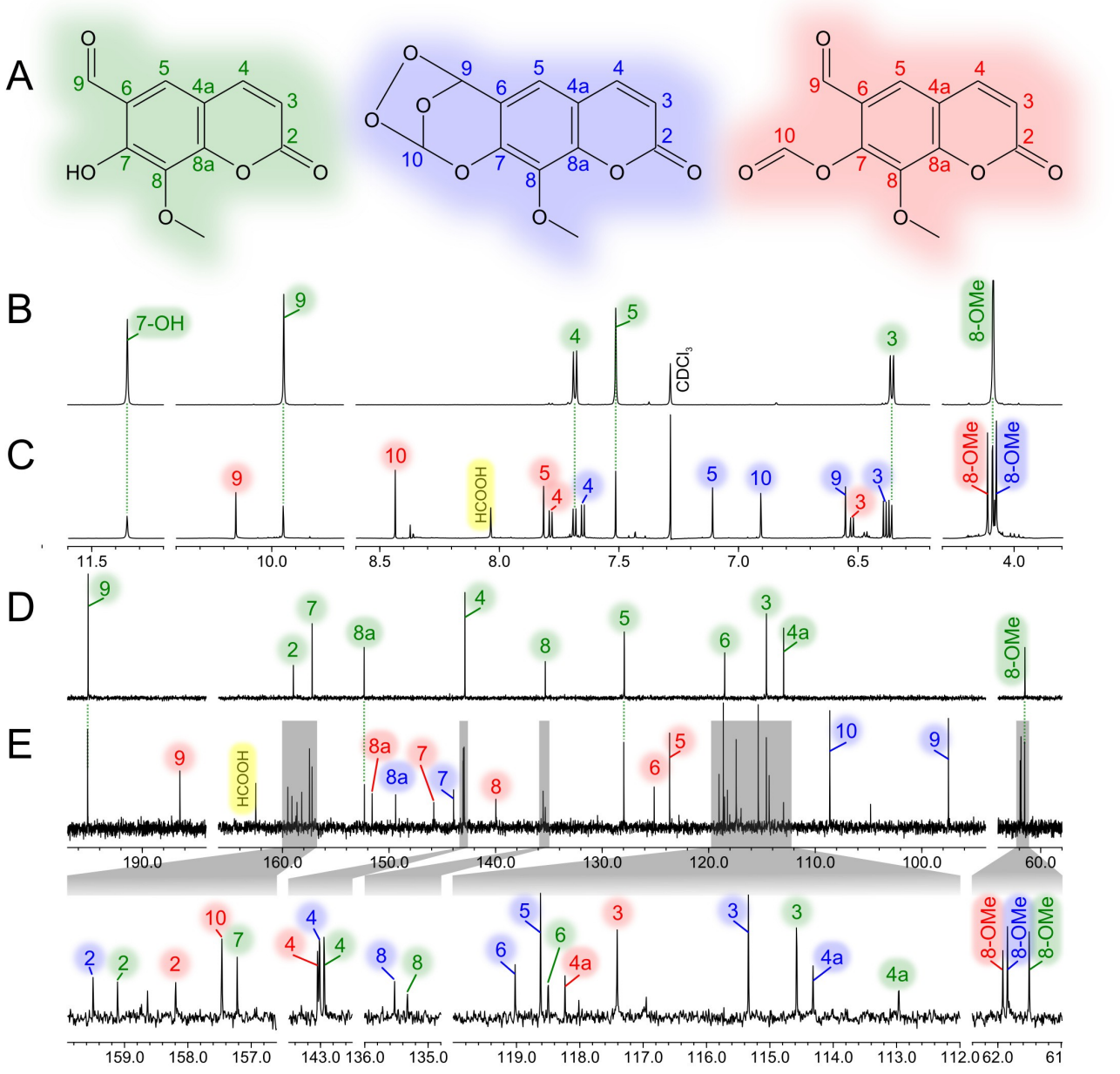
B. 1H NMR spectrum of product mixture treated with Me_2S.

C. 1H NMR spectrum of product mixture processed without addition of Me_2S.

D. 13C NMR spectrum of product mixture treated with Me_2S

Mixtures non-treated with Me_2S contain trioxolane and formic acid. At the same time, amount of common product is very low.

Figure S4. 8-methoxypsoralen ozonolysis products



A. Products of 8-methoxypsoralen ozonolysis. Common, uncommon and trioxolane products are highlighted with red, green and blue color respectively.

B. 1H NMR spectrum of product mixture treated with Me_2S.

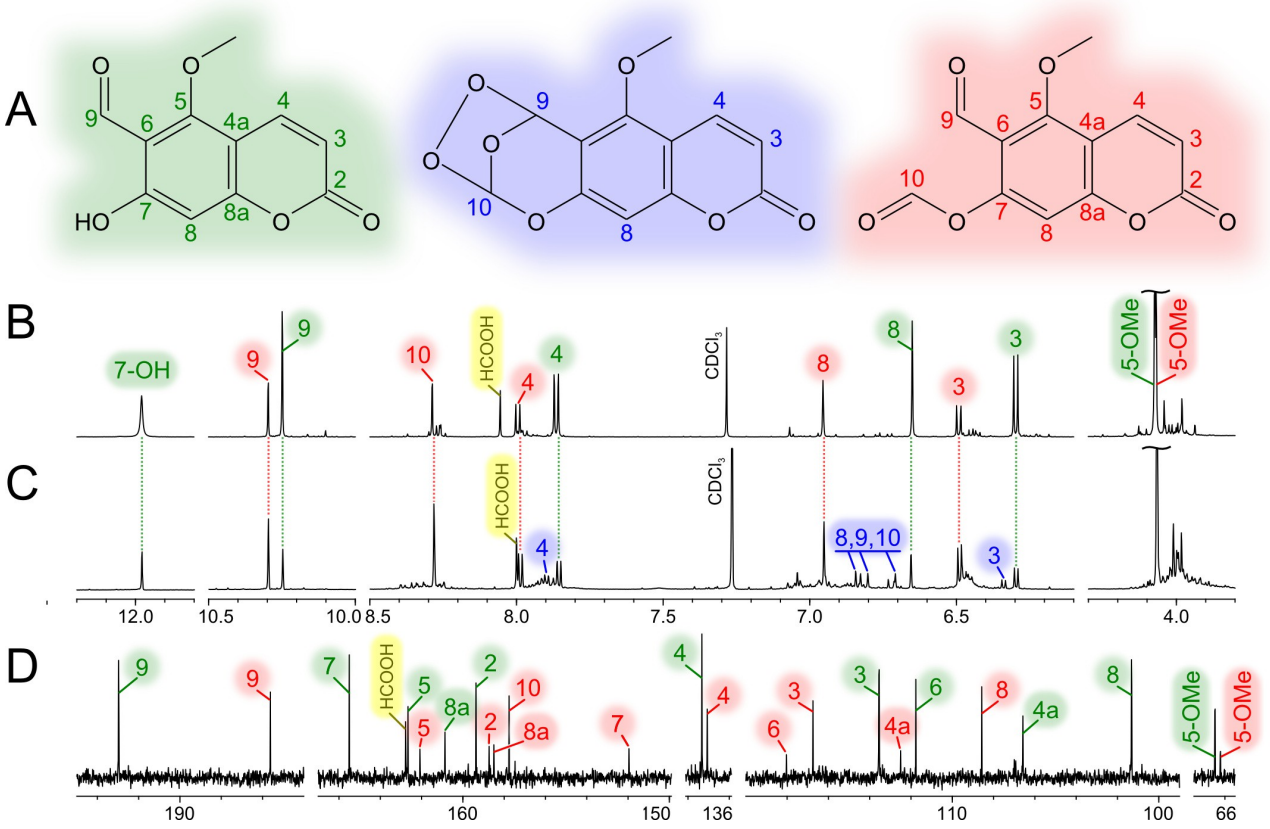
C. 1H NMR spectrum of product mixture processed without addition of Me_2S.

D. 13C NMR spectrum of product mixture treated with Me_2S

E. 13C NMR spectrum of product mixture processed without addition of Me_2S.

Reductive workup with Me_2S yields uncommon product almost exclusively. Mixtures non-treated with Me_2S contain trioxolane, common product and formic acid.

Figure S5. 5-methoxypsoralen ozonolysis products



A. Products of 5-methoxypsoralen ozonolysis. Common, uncommon and trioxolane products are highlighted with red, green and blue color respectively.

B. 1H NMR spectrum of product mixture treated with Me_2S.

C. 1H NMR spectrum of product mixture processed without addition of Me_2S.

D. 13C NMR spectrum of product mixture treated with Me_2S

The product composition is very close to that obtained for psoralen ozonolysis (Fig. S2), but formic acid is always present.

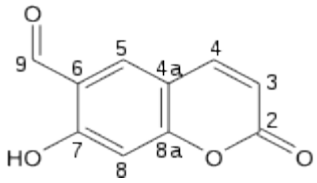
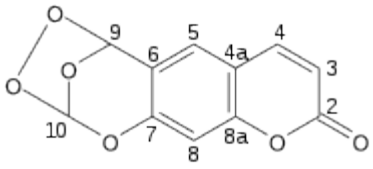
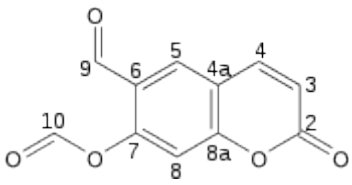
Identification

NMR spectra of reaction mixtures were acquired on Bruker Avance 700 MHz NMR spectrometer equipped with PATXI gradient probe. The following spectra were acquired to confirm chemical structures of individual compounds in reaction mixtures: ^{1}H, ^{13}C, 2D COSY, 2D ^{13}C-HSQC and 2D ^{13}C-HMBC. Proton and carbon resonances were unambiguously assigned on the basis of characteristic chemical shifts, ^{1}H multiplicities and/or COSY cross-peaks and long-range HMBC connectivities. Proton and carbon chemical shifts of unstable ozonides were assigned using characteristic proton/carbon chemical shifts and multiplicities. Chemical shifts of individual compounds are summarized in tables S1-S4 and figures S1-S4.

An Elite Orbitrap mass (Thermo Fisher Scientific, Bremen, Germany) equipped with a HESI ion source was operated in positive mode with a spray voltage of 4 kV. Sheath and auxiliary gas pressure were set to 25 and 5 arbitrary units, correspondingly. Survey scan MS data (from m/z 100–1200) were acquired in the Orbitrap at resolving power of 120K (at m/z 400) at direct infusion rate of 5 µl/min. For accurate mass measurements, the lock-mass function with m/z 445.120025 in positive mode was enabled for MS experiments for internal recalibration in real time. For all MS data acquired, 50 scans were collected and the injection time varied from 50 to 800 ms.

Table S1. Products of psoralen ozonolysis

(chemical shifts in $CDCl_3$)

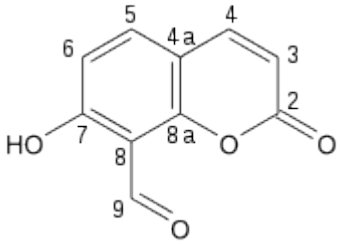
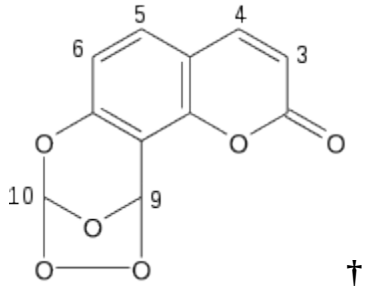
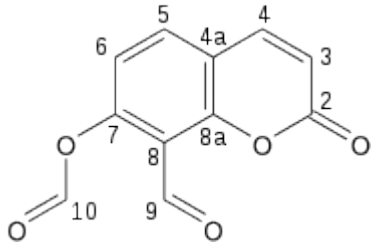
Heavy atom	**6-formyl-7-hydroxy-coumarin**		**2',4'-epidioxy-1',3'-dioxano[5',6':6,7]coumarin**		**6-formyl-7-formyloxy-coumarin**	
	 MH+ found: 191.03354, calc.: 191.03388		 †			
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
2	—	159.49	—	157.55*	—	158.75
3	6.354 d (*J*=9.6Hz)	114.60	6.392 d (*J*=9.6Hz)	115.39	6.526 d (*J*=9.6Hz)	117.65
4	7.768 d (*J*=9.6Hz)	142.44	7.671 d (*J*=9.6Hz)	142.56	7.794 d (*J*=9.6Hz)	142.25
4a	—	112.59	—	113.74	—	117.37
5	7.745 s	134.48	7.375 s	124.92	8.102 s	130.72
6	—	118.29	—	118.74	—	124.60
9	9.944 s	194.90	6.571 s	97.53	10.184 s	186.20
7	—	164.45	—	151.47	—	152.62
7-OH 10	11.414 s	—	6.948 s	108.70	8.422 s	157.50
8	6.903 s	105.20	6.844 s	104.88	7.291 s	111.84
8a	—	159.78	—	156.62*	—	157.92

† Atom numbering on the picture is simplified to fit atom numbering in other products

* Assignment is ambiguous

Table S2. Products of angelicin ozonolysis

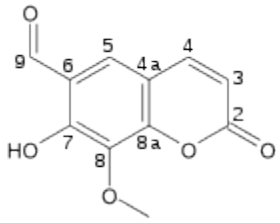
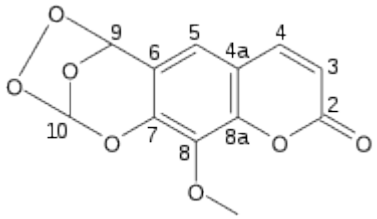
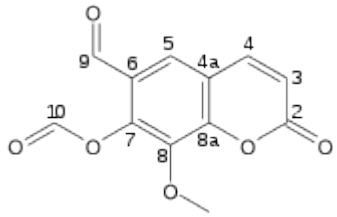
(chemical shifts in $CDCl_3$)

Heavy atom	**7-hydroxy-8-formyl-coumarin**		**2',4'-epidioxy-1',3'-dioxano[5',6':7,8]coumarin**	**7-formyloxy-8-formyl-coumarin**	
	 MH+ found: 191.03369, calc.: 191.03388		 †		
	^{1}H	^{13}C	^{1}H	^{1}H	^{13}C
2	—	159.08	—	—	158.16
3	6.344 d (*J*=9.5Hz)	113.37	6.361 d (*J*=9.6Hz)	6.530 d (*J*=9.7Hz)	116.91
4	7.672 d (*J*=9.5Hz)	143.34	7.684 d (*J*=9.6Hz)	7.771 d (*J*=9.7Hz)	142.42
4a	—	110.86	—	—	117.69
5	7.614 d (*J*=8.7Hz)	135.96	7.500 d (*J*=8.5Hz)	7.756 d (*J*=8.3Hz)	133.57
6	6.905 d (*J*=8.7Hz)	114.57	6.903 d (*J*=8.5Hz)	7.127 d (*J*=8.3Hz)	119.73
7	—	165.51	—	—	150.73
7-OH 10	12.226 s	—	7.131 s	8.259 s	157.83
8	—	108.65	—	—	115.89
8a	—	156.76	—	—	156.50
9	10.618 s	192.92	6.850 s	10.666 s	185.34

† Atom numbering on the picture is simplified to fit atom numbering in other products

Table S3. Products of 8-methoxypsoralen ozonolysis

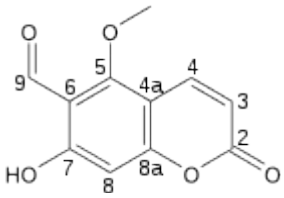
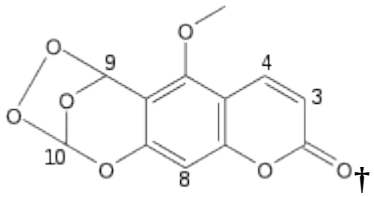
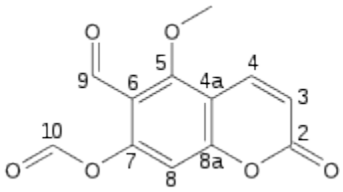
(chemical shifts in $CDCl_3$)

Heavy atom	**6-formyl-7-hydroxy-8-methoxycoumarin**		**2',4'-epidioxy-1',3'-dioxano[5',6':6,7]-8-methoxy coumarin**		**6-formyl-7-formyloxy-8-methoxycoumarin**	
	 MH+ found: 221.04416, calc.: 221.04499		 †			
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
2	—	158.95	—	159.48	—	158.19
3	6.359 d (*J*=9.6Hz)	114.54	6.385 d (*J*=9.6Hz)	115.34	6.524 d (*J*=9.8Hz)	117.41
4	7.684 d (*J*=9.6Hz)	142.81	7.647 d (*J*=9.6Hz)	143.01	7.782 d (*J*=9.8Hz)	143.03
4a	—	112.92	—	114.31	—	118.23
5	7.513 s	127.86	7.106 s	118.61	7.811 s	123.65
6	—	118.44	—	119.01	—	125.10
9	9.950 s	195.03	6.551 d (J=0.9Hz)	97.46	10.146 s	186.46
7	—	157.17	—	143.95	—	145.78
7-OH 10	11.345 s	—	6.904 d (J=0.9Hz)	108.63	8.432 s	157.46
8	—	135.29	—	135.48	—	139.96
8-OMe	4.088 s	61.39	7.070 s	61.82	4.114 s	61.91
8a	—	152.26	—	149.34	—	151.57

† Atom numbering on the picture is simplified to fit atom numbering in other products

Table S4. Products of 5-methoxypsoralen ozonolysis

(chemical shifts in $CDCl_3$)

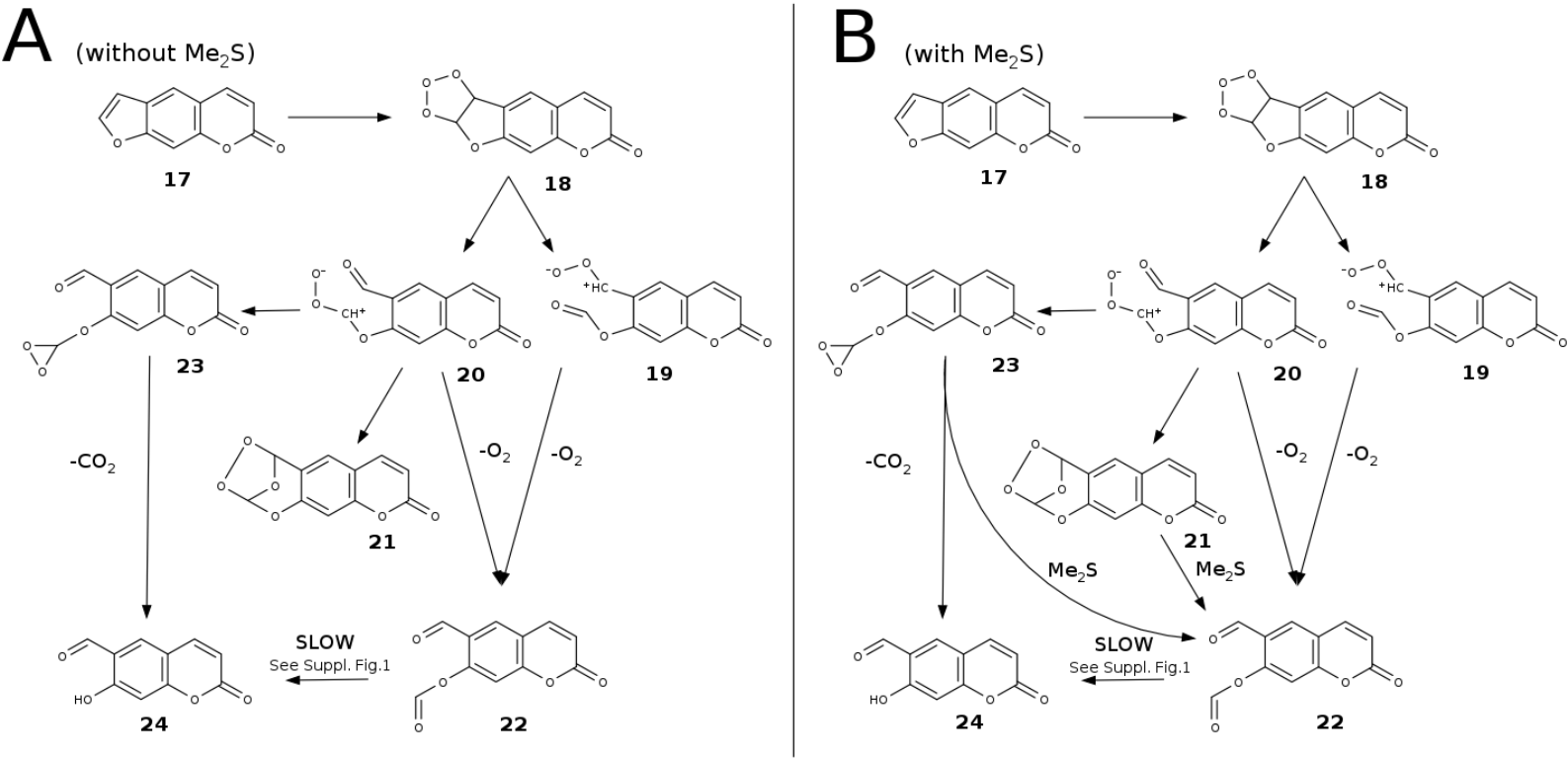
Heavy atom	**5-methoxy-6-formyl-7-hydroxycoumarin**		**2',4'-epidioxy-1',3'-dioxano[5',6':6,7]-5-methoxycoumarin**	**5-methoxy-6-formyl-7-formyloxycoumarin**	
	 MH+ found: 221.0438, calc.: 221.0444		 †		
	^{1}H	^{13}C	^{1}H	^{1}H	^{13}C
2	—	159.36	—	—	158.74
3	6.297 d (*J*=9.8Hz)	113.56	6.339 d (*J*=9.5Hz)	6.492 d (*J*=9.8Hz)	116.77
4	7.862 d (*J*=9.8Hz)	137.33	7.884 d (*J*=9.5Hz)	7.990 d (*J*=9.8Hz)	137.07
4a	—	106.57	—	—	112.50
5	—	162.66	—	—	162.12
5-OMe	4.073 s	66.50	4.011 s	4.069 s	66.19
6	—	111.75	—	—	118.04
9	10.250 s	192.95	6.710 s*	10.300 s	185.60
7	—	165.49	—	—	151.95
7-OH 10	12.226 s	—	6.845 s*	8.286 s	157.75
8	6.694 s	101.33	6.803 s*	6.960 s	108.58
8a	—	160.84	—	—	158.47

† Atom numbering on the picture is simplified to fit atom numbering in other products

* Assignment is ambiguous

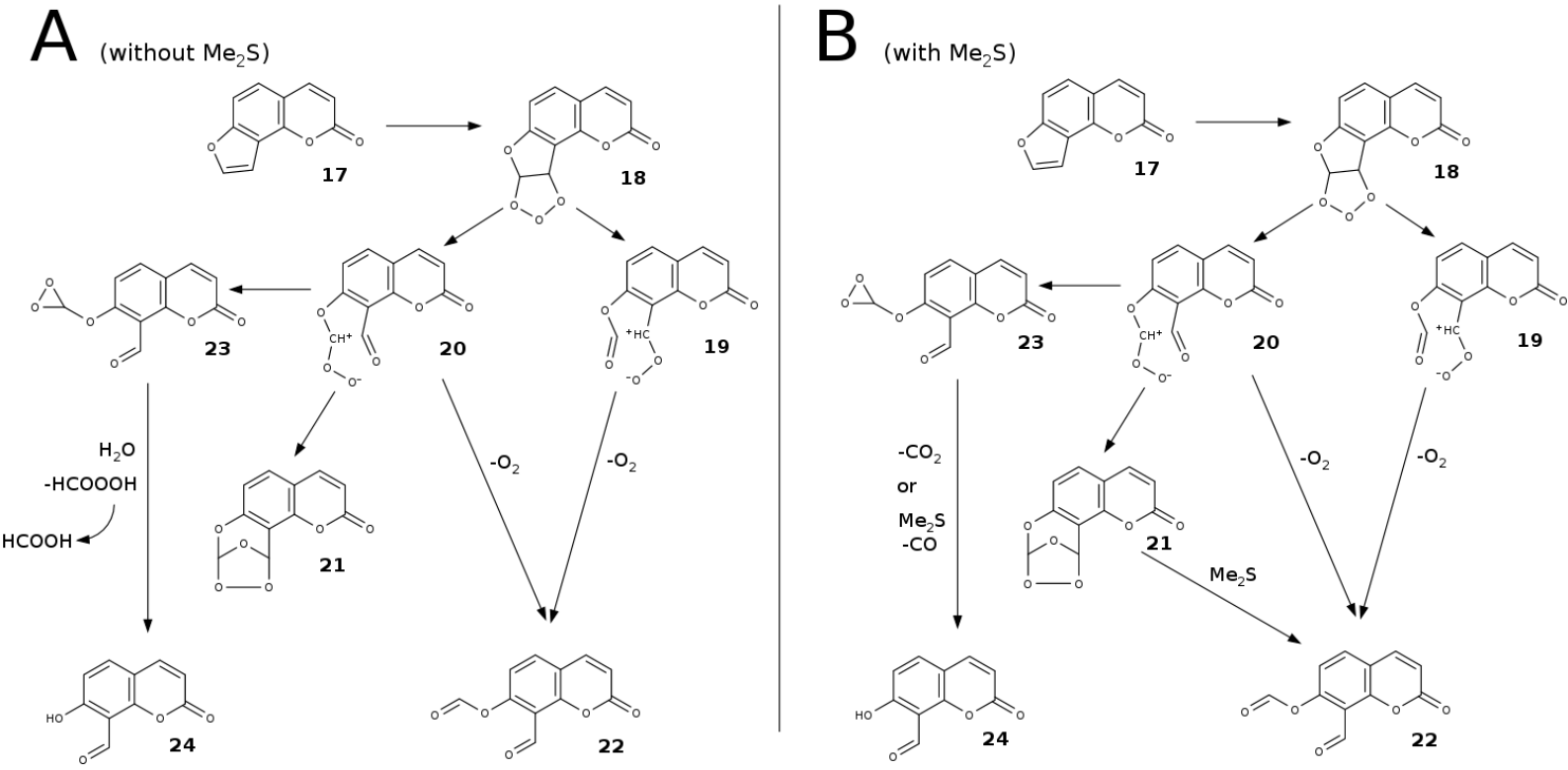
Proposed mechanism (unfolded schemes)

Scheme S1. Psoralen ozonolysis



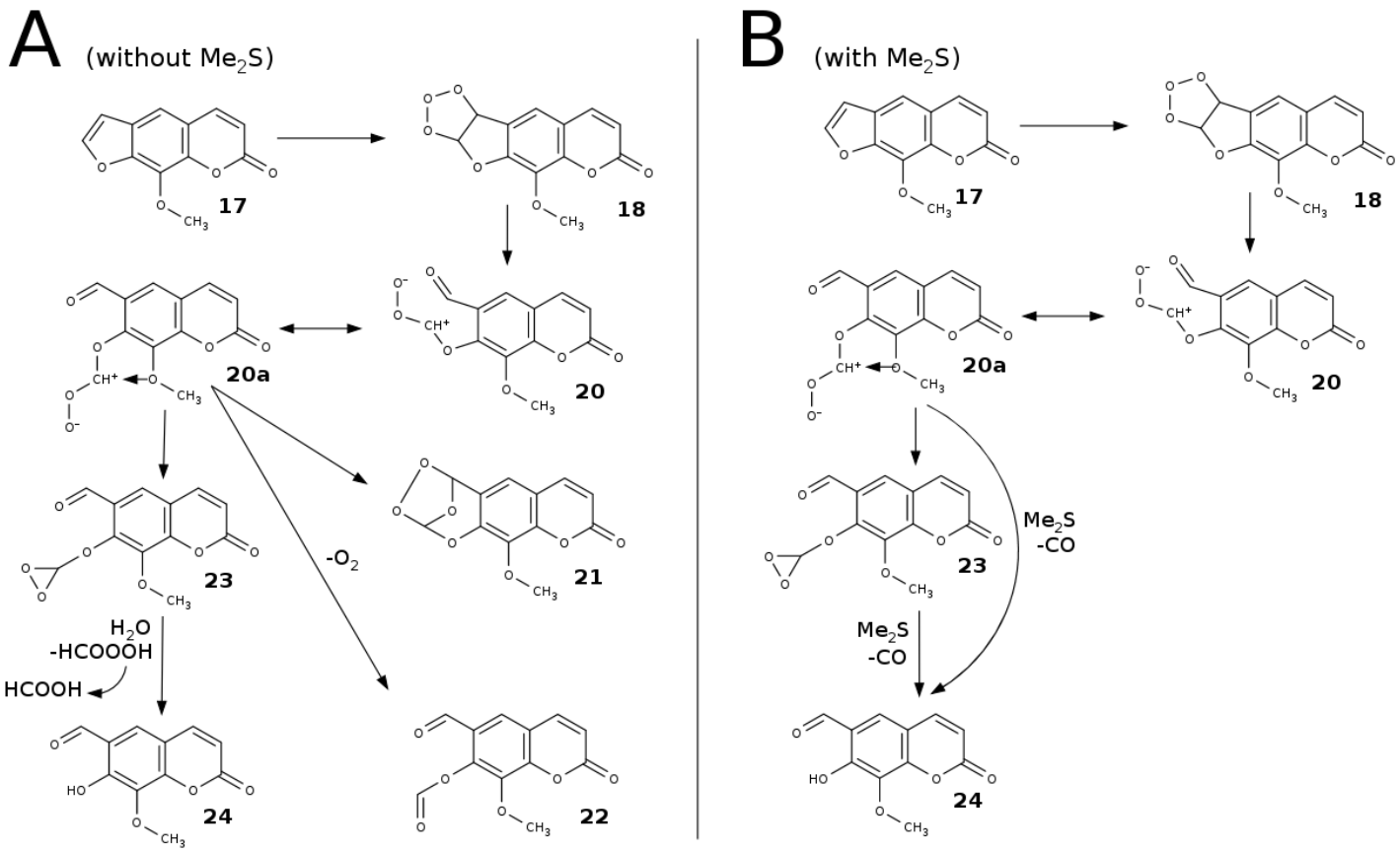
Both common (22) and uncommon (24) products are obtained regardless of Me_2S work-up. Trioxolane (21) is obtained only without adding of Me_2S (Scheme A). Since no formic acid is found among products (Fig. S2), the dioxirane (23) is not hydrolyzed but decomposes with CO_2 release.

Scheme S2. Angelicin ozonolysis



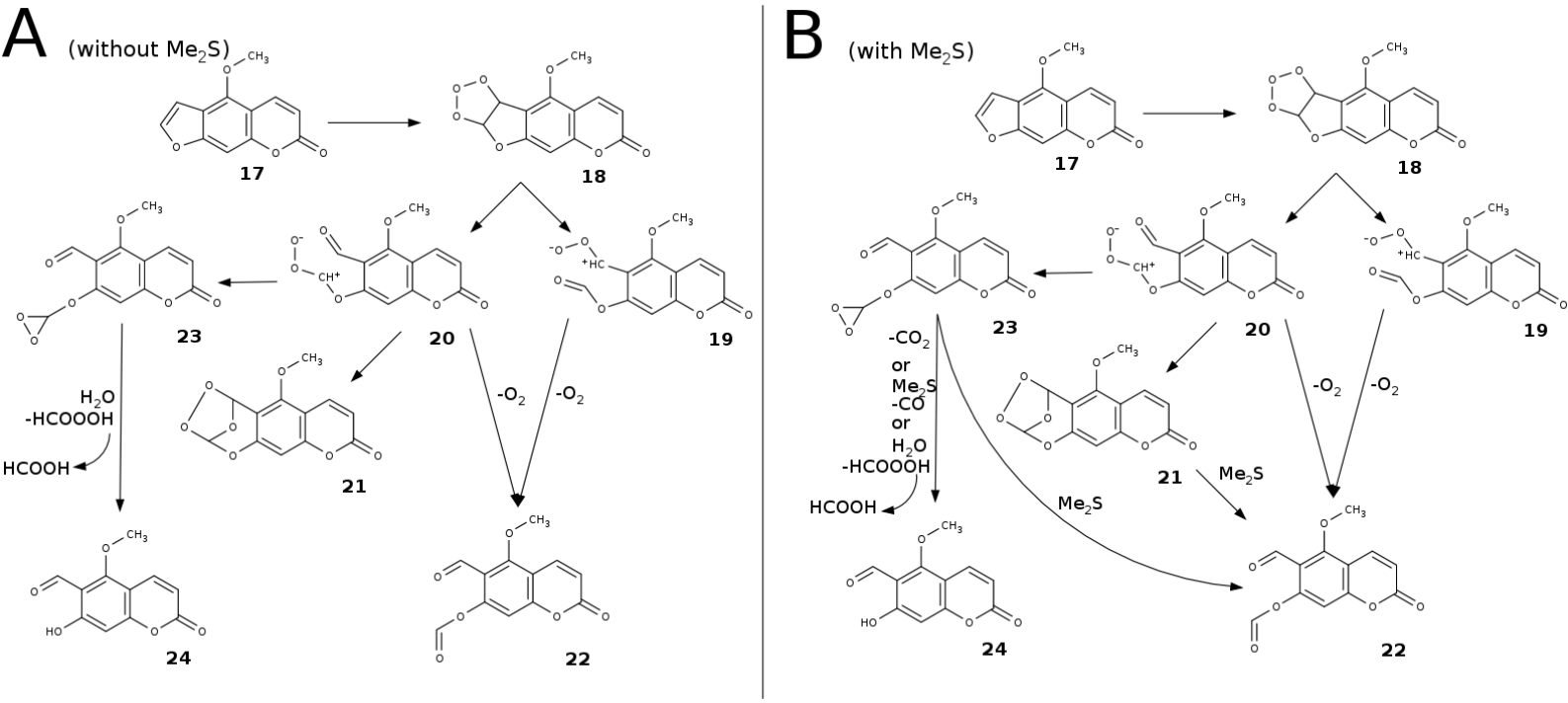
Both common (22) and uncommon (24) products are obtained regardless of Me_2S work-up. Trioxolane (21) is obtained only without adding of Me_2S (Scheme A). Formic acid is found in reaction mixture lacking Me_2S work-up (Fig. S3). We suggest that it is produced by hydrolysis of dioxirane (23) with traces of water. After Me_2S work-up dioxirane (23) is reduced to uncommon product 24 (Scheme B).

Scheme S3. 8-methoxypsoralen ozonolysis



Due to the stabilization of carbonyl oxide with methoxy group (structure 20a) primary ozonide opens with predominant formation of carbonyl oxide 20. After Me_2S work-up it reduce to uncommon product 24, both directly or through dioxirane 23. In this case, compound 24 is the only product of ozonolysis. Formic acid is not formed. In the absence of Me_2S stabilized carbonyl oxide 20a can either convert to trioxolane 21 or bimolecularly loose O_2 yielding common product 22 or undergo hydrolysis with traces of water forming uncommon product 24 and formic acid. All these are found in reaction mixture – see Fig. S4.

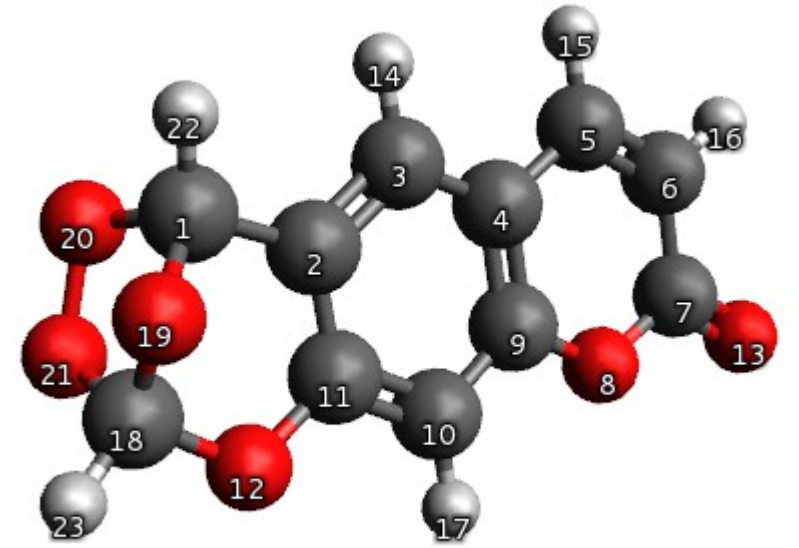
Scheme S4. 5-methoxypsoralen ozonolysis



Product distribution is very similar to that obtained for psoralen ozonolysis (Scheme S1), but dioxirane 23 seems to be more labile and hydrolyze releasing formic acid.

Additional data (Hartree–Fock calculation output)

1,2,4-Trioxolane from psoralen



d1_uhf.log part

Bonds geometry

! Name	Definition	Value	Derivative Info.
! R1	R(1,2)	1.5057	-DE/DX = 0.0
! R2	R(1,19)	1.3977	-DE/DX = 0.0
! R3	R(1,20)	1.3975	-DE/DX = 0.0
! R4	R(1,22)	1.0763	-DE/DX = 0.0
! R5	R(2,3)	1.3723	-DE/DX = 0.0
! R6	R(2,11)	1.3998	-DE/DX = 0.0
! R7	R(3,4)	1.3946	-DE/DX = 0.0
! R8	R(3,14)	1.0764	-DE/DX = 0.0
! R9	R(4,5)	1.4504	-DE/DX = 0.0
! R10	R(4,9)	1.391	-DE/DX = 0.0
! R11	R(5,6)	1.33	-DE/DX = 0.0
! R12	R(5,15)	1.0757	-DE/DX = 0.0
! R13	R(6,7)	1.4663	-DE/DX = 0.0
! R14	R(6,16)	1.0718	-DE/DX = 0.0
! R15	R(7,8)	1.3595	-DE/DX = 0.0
! R16	R(7,13)	1.1819	-DE/DX = 0.0
! R17	R(8,9)	1.3466	-DE/DX = 0.0
! R18	R(9,10)	1.3858	-DE/DX = 0.0
! R19	R(10,11)	1.3747	-DE/DX = 0.0
! R20	R(10,17)	1.0721	-DE/DX = 0.0
! R21	R(11,12)	1.3543	-DE/DX = 0.0
! R22	R(12,18)	1.3871	-DE/DX = 0.0
! R23	R(18,19)	1.3674	-DE/DX = 0.0
! R24	R(18,21)	1.397	-DE/DX = 0.0
! R25	R(18,23)	1.0722	-DE/DX = 0.0
! R26	R(20,21)	1.4092	-DE/DX = 0.0

Mulliken atomic charges:

		1
1	C	0.329997
2	C	-0.030107
3	C	-0.179716
4	C	-0.100819
5	C	-0.079599
6	C	-0.369109
7	C	0.818199
8	O	-0.678819
9	C	0.441631
10	C	-0.305937
11	C	0.446918
12	O	-0.670526
13	O	-0.542158
14	H	0.233815
15	H	0.235735
16	H	0.244638
17	H	0.261746
18	C	0.715306
19	O	-0.593780
20	O	-0.309137
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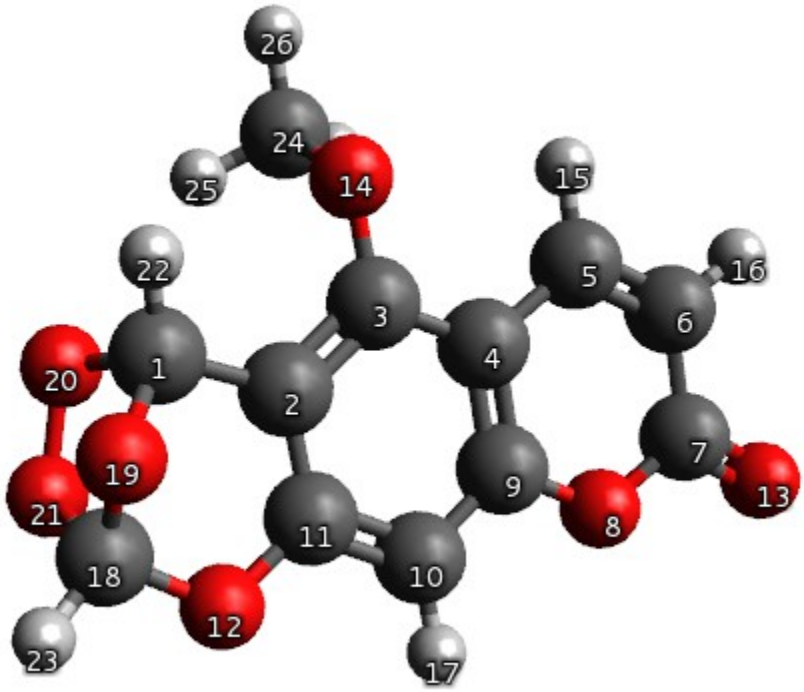
22	H	0.245562
23	H	0.248115

1,2,4-Trioxolane from 5-methoxypsoralen



d2_uhf.log part

Bonds geometry

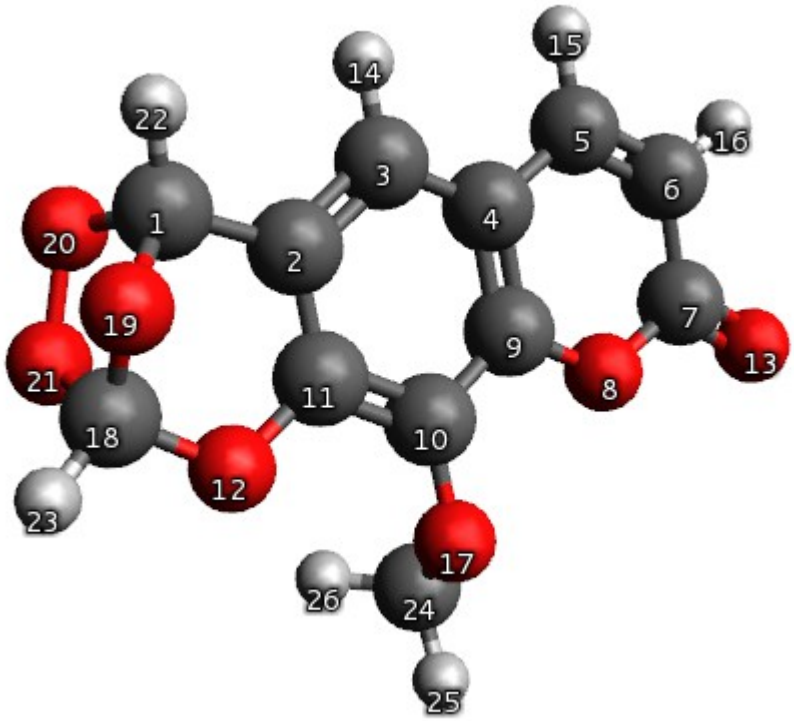
! Name	Definition	Value	Derivative Info.
! R1	R(1,2)	1.5049	-DE/DX = 0.0 !
! R2	R(1,19)	1.398	-DE/DX = 0.0 !
! R3	R(1,20)	1.3989	-DE/DX = 0.0 !
! R4	R(1,22)	1.0747	-DE/DX = 0.0 !
! R5	R(2,3)	1.3763	-DE/DX = 0.0 !
! R6	R(2,11)	1.3985	-DE/DX = 0.0 !
! R7	R(3,4)	1.3984	-DE/DX = 0.0 !
! R8	R(3,14)	1.3546	-DE/DX = 0.0 !
! R9	R(4,5)	1.4494	-DE/DX = 0.0 !
! R10	R(4,9)	1.392	-DE/DX = 0.0 !
! R11	R(5,6)	1.3306	-DE/DX = 0.0 !
! R12	R(5,15)	1.0734	-DE/DX = 0.0 !
! R13	R(6,7)	1.4648	-DE/DX = 0.0 !
! R14	R(6,16)	1.0718	-DE/DX = 0.0 !
! R15	R(7,8)	1.3611	-DE/DX = 0.0 !
! R16	R(7,13)	1.1818	-DE/DX = 0.0 !
! R17	R(8,9)	1.345	-DE/DX = 0.0 !
! R18	R(9,10)	1.3852	-DE/DX = 0.0 !
! R19	R(10,11)	1.3749	-DE/DX = 0.0 !
! R20	R(10,17)	1.0717	-DE/DX = 0.0 !
! R21	R(11,12)	1.3528	-DE/DX = 0.0 !
! R22	R(12,18)	1.3877	-DE/DX = 0.0 !
! R23	R(14,24)	1.4183	-DE/DX = 0.0 !
! R24	R(18,19)	1.3657	-DE/DX = 0.0 !

! R25	R(18,21)	1.3991	-DE/DX =	0.0	!
! R26	R(18,23)	1.0722	-DE/DX =	0.0	!
! R27	R(20,21)	1.4092	-DE/DX =	0.0	!
! R28	R(24,25)	1.0826	-DE/DX =	0.0	!
! R29	R(24,26)	1.0791	-DE/DX =	0.0	!
! R30	R(24,27)	1.0836	-DE/DX =	0.0	!

Mulliken atomic charges:

		1
1	C	0.336394
2	C	-0.092590
3	C	0.422191
4	C	-0.154061
5	C	-0.067473
6	C	-0.373730
7	C	0.818482
8	O	-0.680051
9	C	0.460673
10	C	-0.314842
11	C	0.475106
12	O	-0.673340
13	O	-0.542784
14	O	-0.682399
15	H	0.250505
16	H	0.243252
17	H	0.259779
18	C	0.717627
19	O	-0.594071
20	O	-0.315137
21	O	-0.364255
22	H	0.262448
23	H	0.248031
24	C	-0.194120
25	H	0.187733
26	H	0.196161
27	H	0.170471

1,2,4-Trioxolane from 8-methoxypsoralen



d3_uhf.log part

Bonds geometry

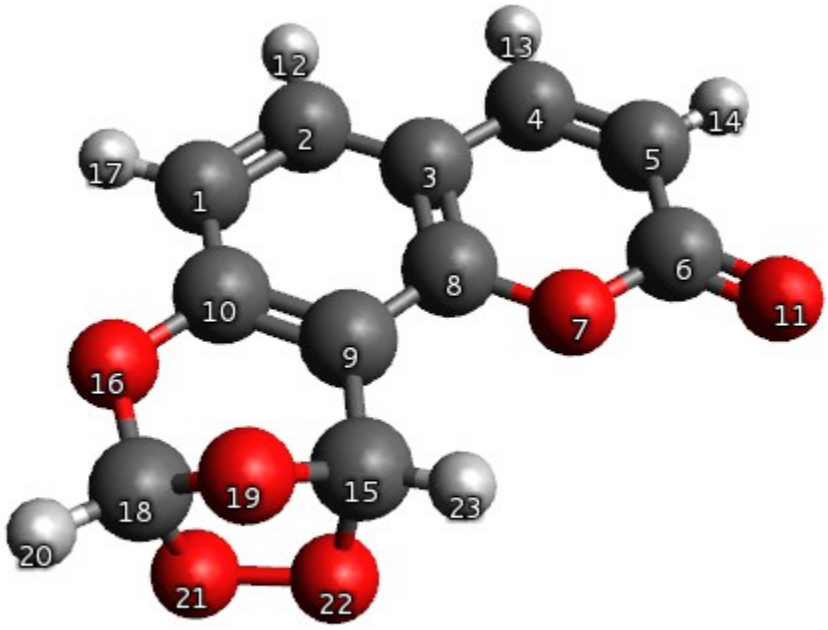
! Name	Definition	Value	Derivative Info.
! R1	R(1,2)	1.5065	-DE/DX = 0.0 !
! R2	R(1,19)	1.3966	-DE/DX = 0.0 !
! R3	R(1,20)	1.3977	-DE/DX = 0.0 !
! R4	R(1,22)	1.0763	-DE/DX = 0.0 !
! R5	R(2,3)	1.3718	-DE/DX = 0.0 !
! R6	R(2,11)	1.3978	-DE/DX = 0.0 !
! R7	R(3,4)	1.3935	-DE/DX = 0.0 !
! R8	R(3,14)	1.076	-DE/DX = 0.0 !
! R9	R(4,5)	1.4514	-DE/DX = 0.0 !
! R10	R(4,9)	1.3899	-DE/DX = 0.0 !
! R11	R(5,6)	1.3296	-DE/DX = 0.0 !
! R12	R(5,15)	1.0756	-DE/DX = 0.0 !
! R13	R(6,7)	1.4666	-DE/DX = 0.0 !
! R14	R(6,16)	1.0718	-DE/DX = 0.0 !
! R15	R(7,8)	1.358	-DE/DX = 0.0 !
! R16	R(7,13)	1.182	-DE/DX = 0.0 !
! R17	R(8,9)	1.3465	-DE/DX = 0.0 !
! R18	R(9,10)	1.3931	-DE/DX = 0.0 !
! R19	R(10,11)	1.3808	-DE/DX = 0.0 !
! R20	R(10,17)	1.3459	-DE/DX = 0.0 !
! R21	R(11,12)	1.3547	-DE/DX = 0.0 !
! R22	R(12,18)	1.385	-DE/DX = 0.0 !
! R23	R(17,24)	1.4137	-DE/DX = 0.0 !
! R24	R(18,19)	1.3677	-DE/DX = 0.0 !
! R25	R(18,21)	1.3981	-DE/DX = 0.0 !
! R26	R(18,23)	1.0722	-DE/DX = 0.0 !

! R27	R(20,21)	1.4093	-DE/DX =	0.0	!
! R28	R(24,25)	1.0792	-DE/DX =	0.0	!
! R29	R(24,26)	1.0836	-DE/DX =	0.0	!
! R30	R(24,27)	1.0827	-DE/DX =	0.0	!

Mulliken atomic charges:

		1
1	C	0.325910
2	C	0.004109
3	C	-0.193327
4	C	-0.064455
5	C	-0.085905
6	C	-0.365558
7	C	0.818018
8	O	-0.671116
9	C	0.376603
10	C	0.308493
11	C	0.393985
12	O	-0.663930
13	O	-0.542977
14	H	0.231872
15	H	0.236173
16	H	0.245252
17	O	-0.652861
18	C	0.717083
19	O	-0.592597
20	O	-0.310104
21	O	-0.364458
22	H	0.245882
23	H	0.249110
24	C	-0.177625
25	H	0.190313
26	H	0.166608
27	H	0.175501

1,2,4-Trioxolane from angelicin



d3_uhf.log part

Bonds geometry

! Name	Definition	Value	Derivative Info.
! R1	R(1,2)	1.376	-DE/DX = 0.0 !
! R2	R(1,10)	1.3888	-DE/DX = 0.0 !
! R3	R(1,17)	1.0727	-DE/DX = 0.0 !
! R4	R(2,3)	1.3956	-DE/DX = 0.0 !
! R5	R(2,12)	1.0754	-DE/DX = 0.0 !
! R6	R(3,4)	1.4501	-DE/DX = 0.0 !
! R7	R(3,8)	1.3896	-DE/DX = 0.0 !
! R8	R(4,5)	1.3309	-DE/DX = 0.0 !
! R9	R(4,13)	1.0756	-DE/DX = 0.0 !
! R10	R(5,6)	1.465	-DE/DX = 0.0 !
! R11	R(5,14)	1.0717	-DE/DX = 0.0 !
! R12	R(6,7)	1.3629	-DE/DX = 0.0 !
! R13	R(6,11)	1.1814	-DE/DX = 0.0 !
! R14	R(7,8)	1.3475	-DE/DX = 0.0 !
! R15	R(8,9)	1.3826	-DE/DX = 0.0 !
! R16	R(9,10)	1.3862	-DE/DX = 0.0 !
! R17	R(9,15)	1.5075	-DE/DX = 0.0 !
! R18	R(10,16)	1.3526	-DE/DX = 0.0 !
! R19	R(15,19)	1.3991	-DE/DX = 0.0 !
! R20	R(15,22)	1.3967	-DE/DX = 0.0 !
! R21	R(15,23)	1.0742	-DE/DX = 0.0 !
! R22	R(16,18)	1.3903	-DE/DX = 0.0 !
! R23	R(18,19)	1.3656	-DE/DX = 0.0 !
! R24	R(18,20)	1.0723	-DE/DX = 0.0 !
! R25	R(18,21)	1.3956	-DE/DX = 0.0 !
! R26	R(21,22)	1.4098	-DE/DX = 0.0 !

Mulliken atomic charges:

		1
1	C	-0.260716
2	C	-0.176871
3	C	-0.080516
4	C	-0.084605
5	C	-0.369899
6	C	0.821069
7	O	-0.694280
8	C	0.435408
9	C	-0.107130
10	C	0.454851
11	O	-0.541288
12	H	0.230125
13	H	0.237834
14	H	0.245415
15	C	0.354484
16	O	-0.673782
17	H	0.238795
18	C	0.715754
19	O	-0.593907
20	H	0.246033
21	O	-0.365554
22	O	-0.304252
23	H	0.273031