Supplementary Materials: One-Pot Synthesis of (+)-Nootkatone via Dark Singlet Oxygenation of Valencene: The Triple Role of the Amphiphilic Molybdate Catalyst

Bing Hong, Raphaël Lebeuf, Stéphanie Delbaere, Paul L. Alsters and Véronique Nardello-Rataj

1. NMR Characterization of Products Obtained from Valencene Photooxidation in Methanol

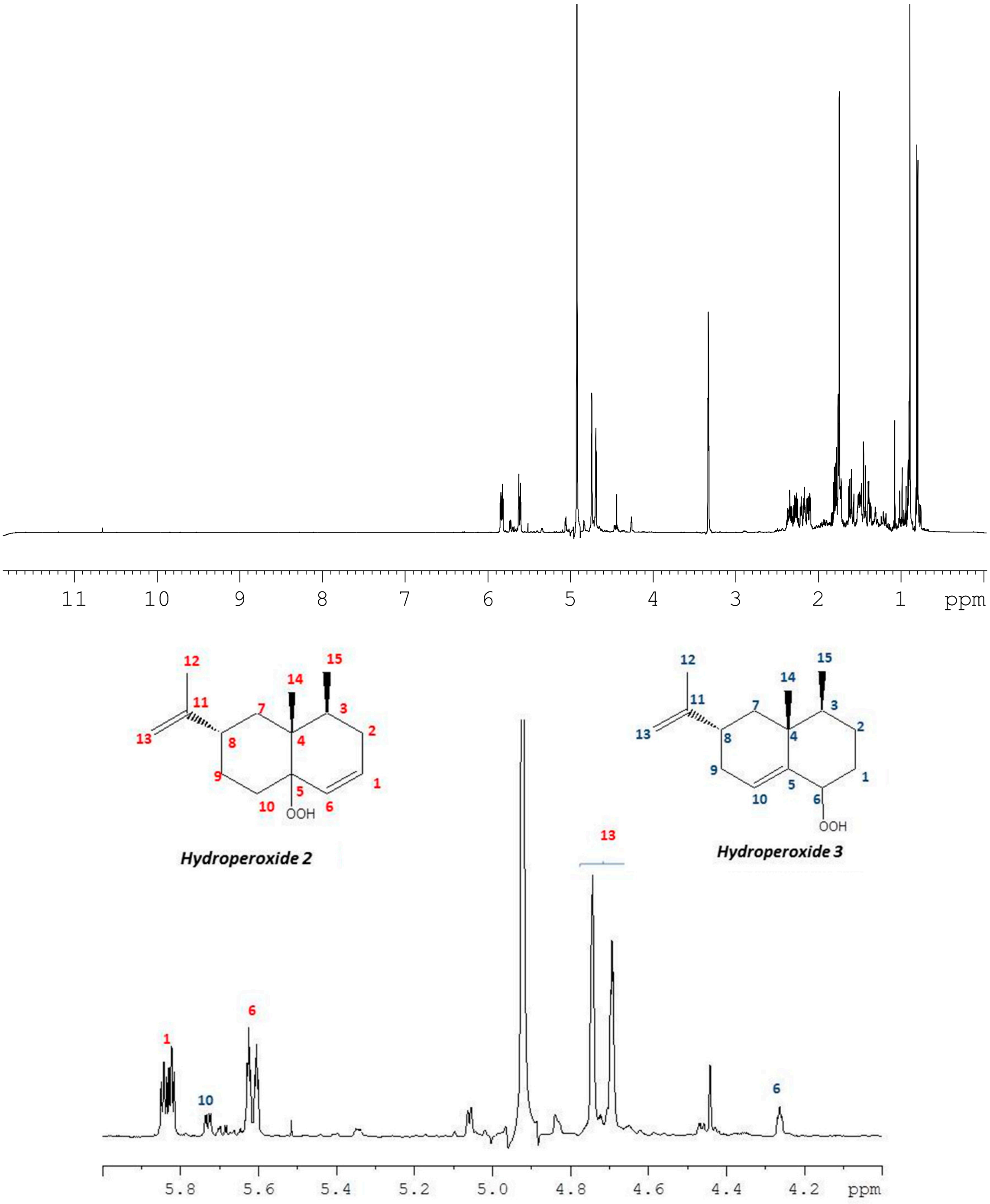


Figure S1. *Cont.*

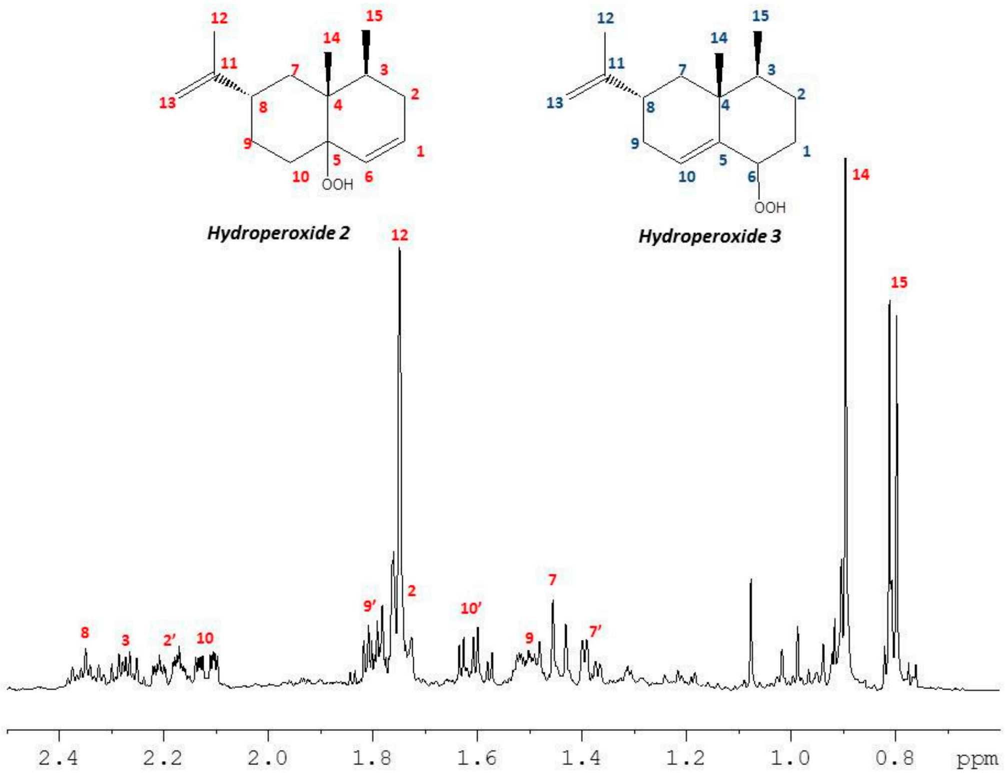


Figure S1. ^{1}H NMR spectrum (in CD_3OD) of products (hydroperoxides **2** and **3**) obtained by photooxidation of valencene in methanol.

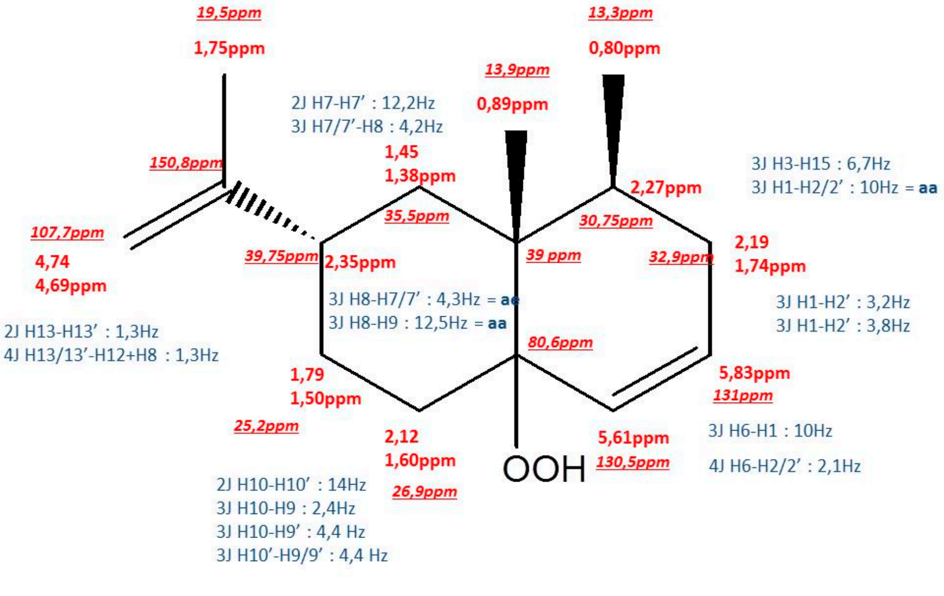


Figure S2. ^{1}H; ^{13}C and ^{1}H-^{1}H NMR (in CD_3OD) data of hydroperoxide **2**.

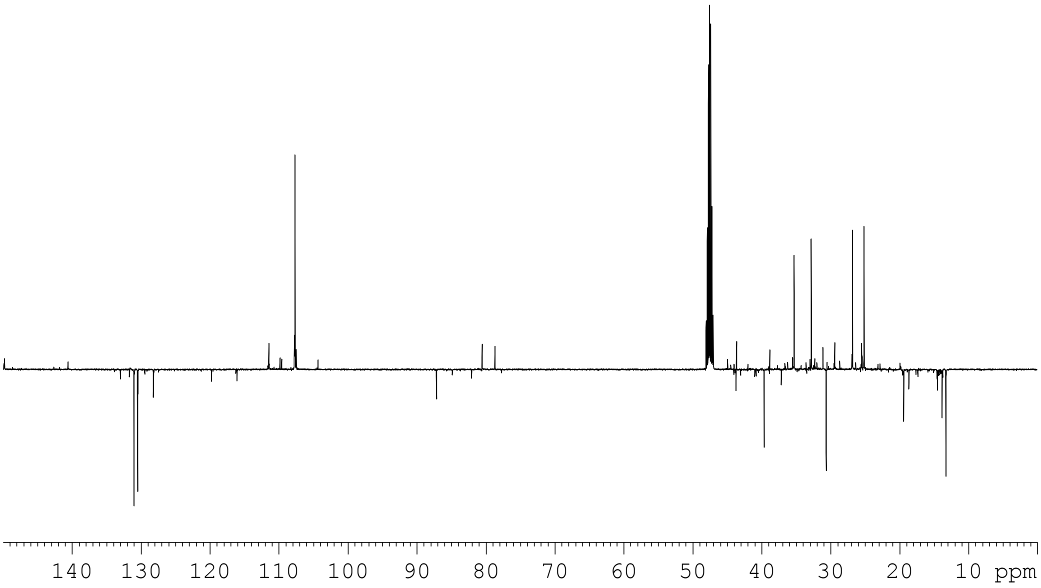


Figure S3. ^{13}C NMR (in CD_3OD) J-mod of products obtained from valencene photooxidation.

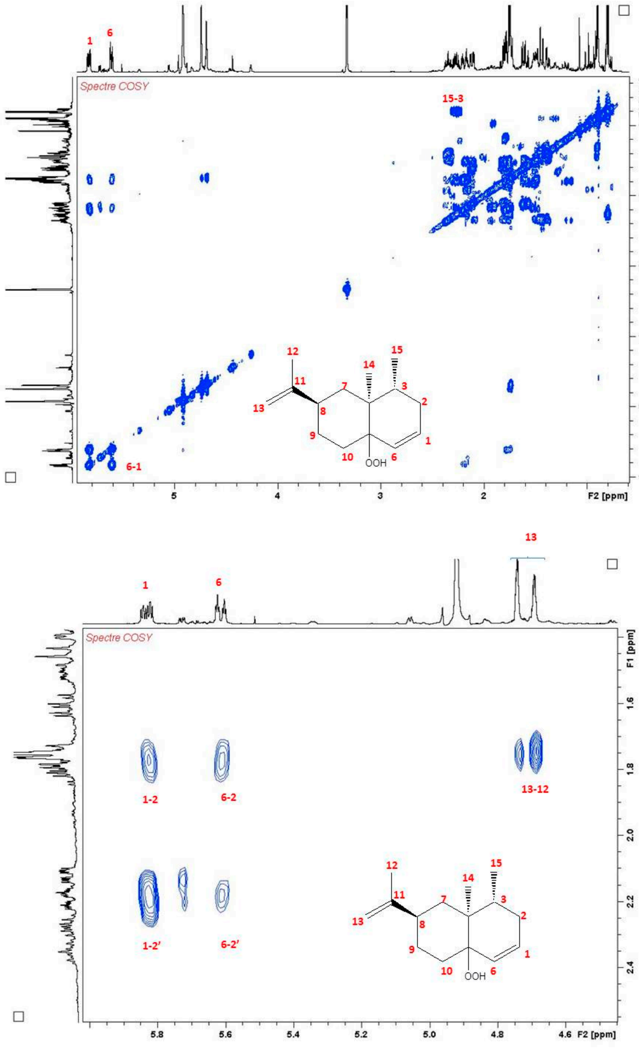


Figure S4. *Cont.*

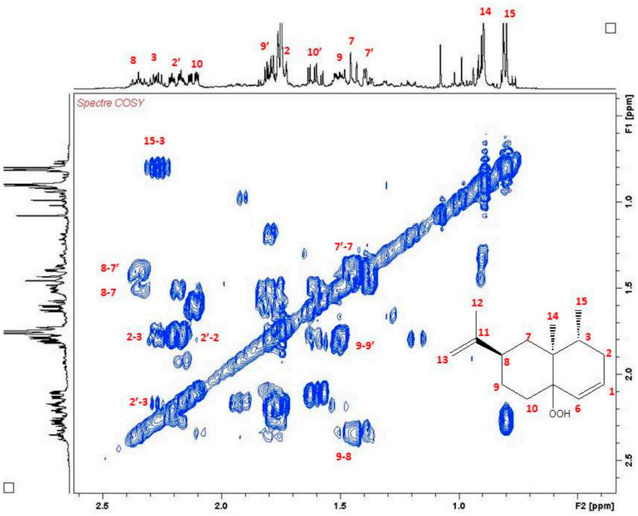


Figure S4. ^{1}H NMR COSY (in CD_3OD) spectrum of products obtained from valencene photooxidation.

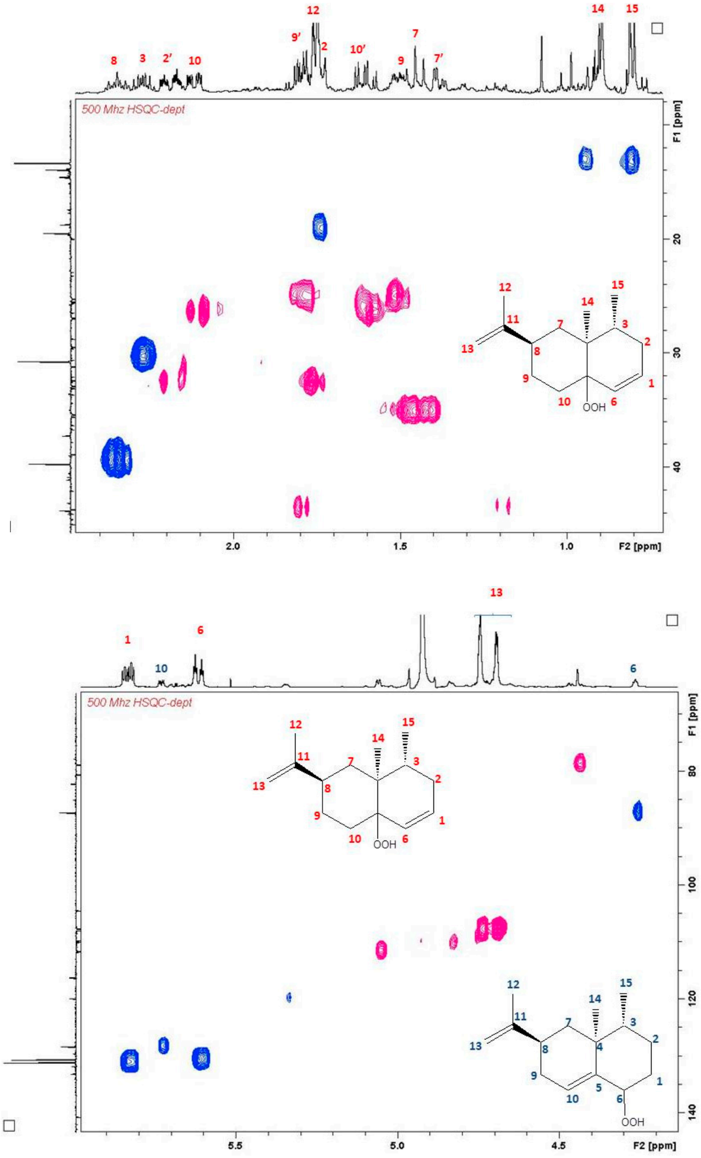


Figure S5. ^{1}H-^{13}C NMR HSQC-dept spectrum (in CD_3OD) of products obtained from valencene photooxidation.

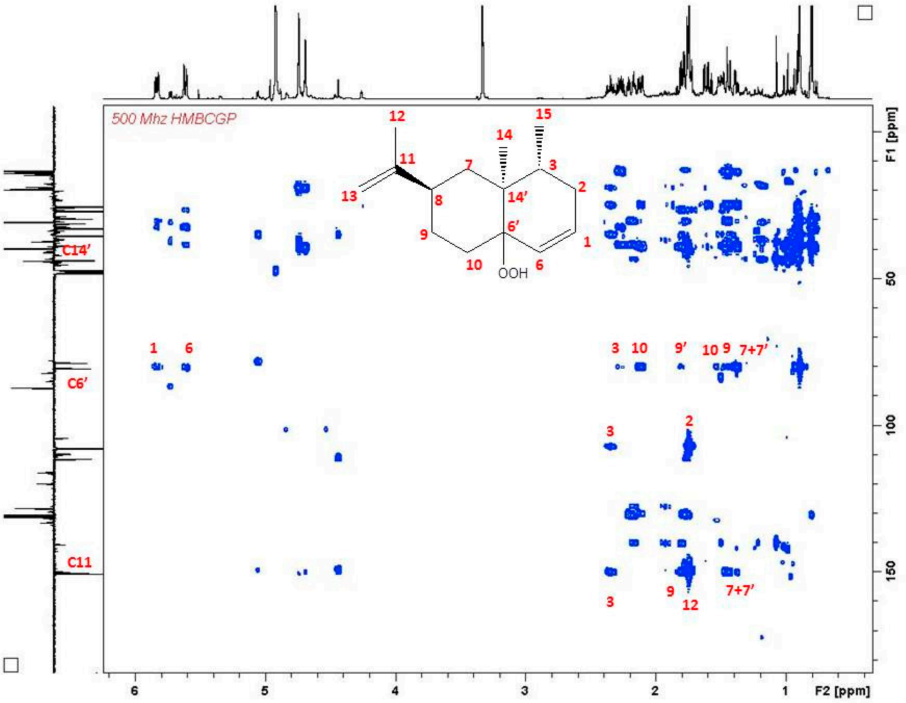


Figure S6. ^{1}H-^{13}C NMR HMBC spectrum (in CD_3OD) of products obtained from valencene photooxidation.

2. NMR Characterization of Hydroperoxide 4 Obtained in Toluene after Rearrangement

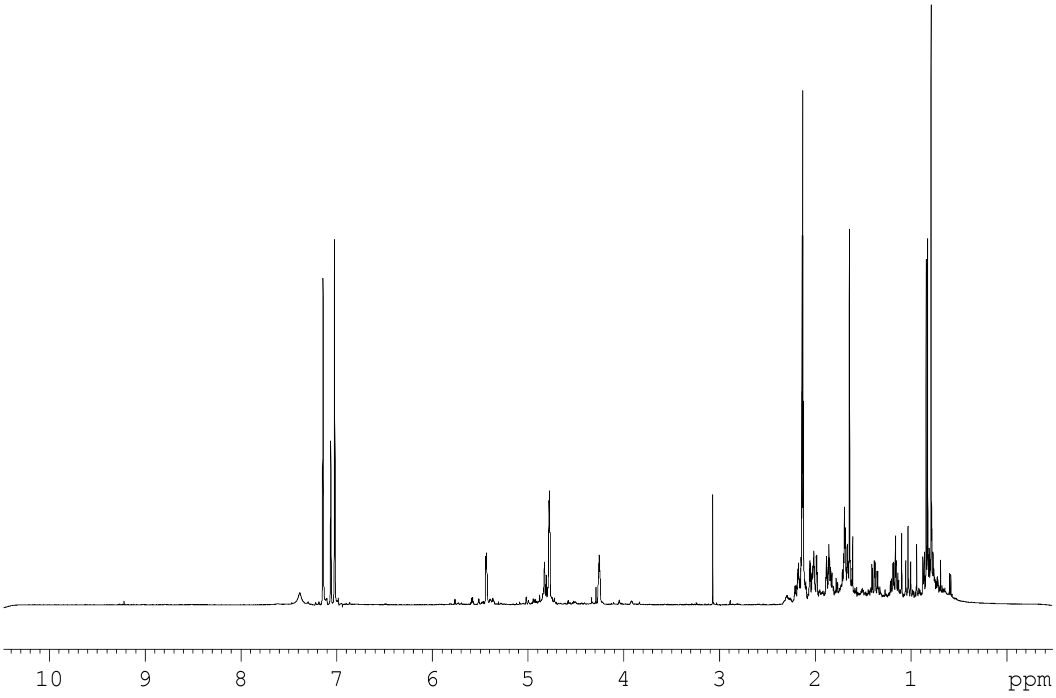


Figure S7. *Cont.*

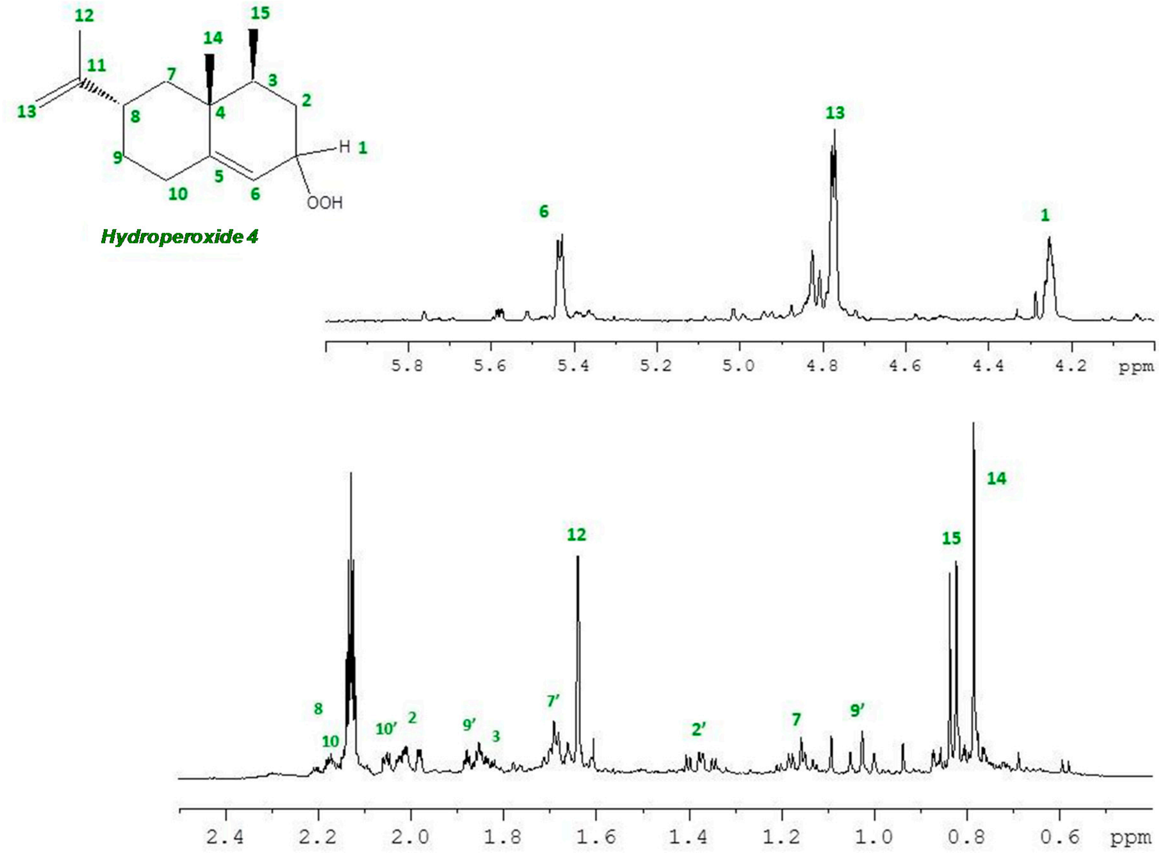


Figure S7. ^{1}H NMR spectrum of hydroperoxide **4** in toluene-d8.

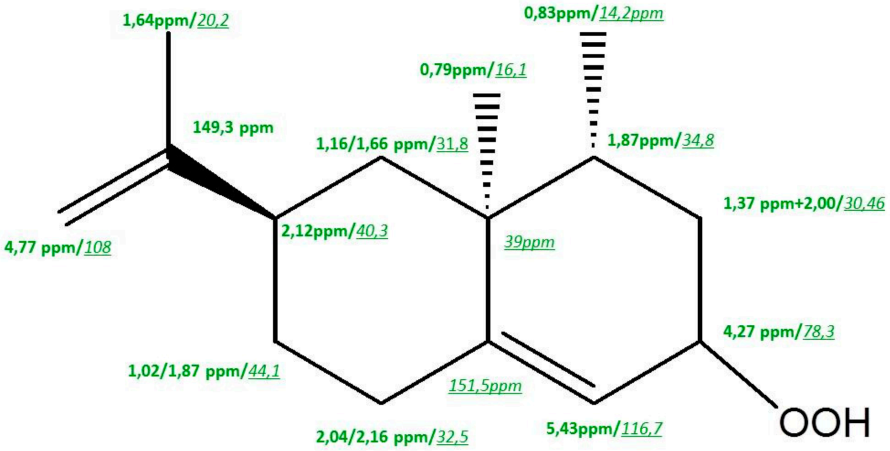


Figure S8. ^{1}H and ^{13}C NMR data of hydroperoxide **4** (in toluene).

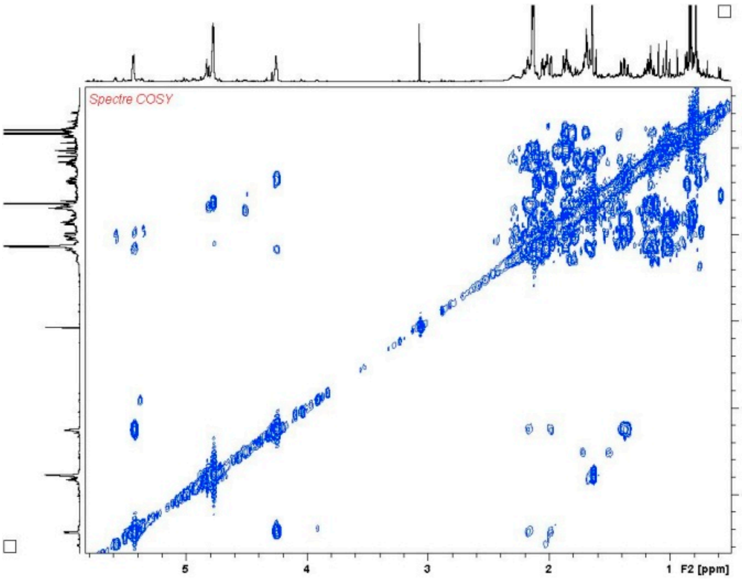


Figure S9. ^{1}H NMR COSY spectrum of hydroperoxide **4** in toluene-d8.

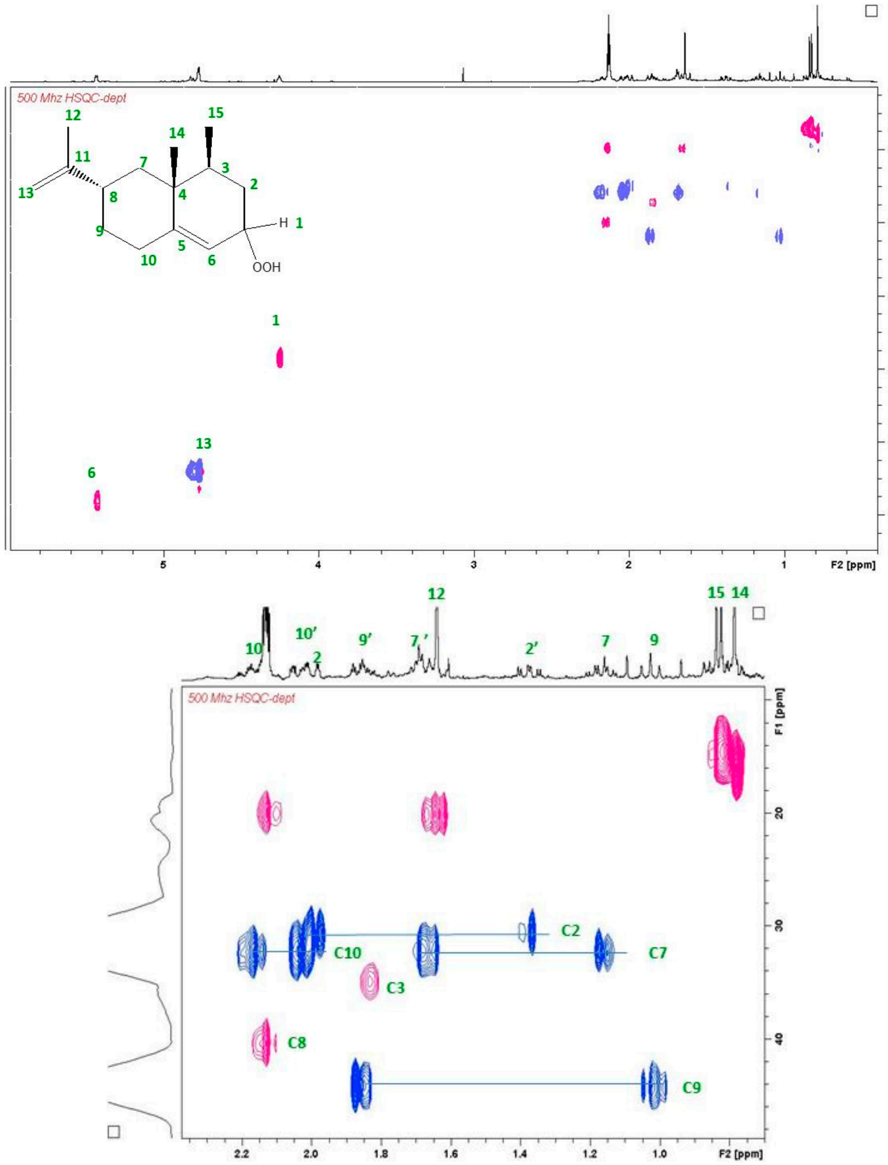


Figure S10. ^{1}H-^{13}C NMR HSQC-dept spectrum of hydroperoxide **4** in toluene-d8.

3. Conversion of Hydroperoxide 2 into Hydroperoxide 4 in Different Solvents

A 10 mL CH_3OH solution with 0.125 mg of Rose Bengal was prepared in a 25 mL special flat flask for photooxidation. Valencene (102 mg, 0.5 mmol) was dissolved, and 5-chloro-1,3-dimethoxybenzene (27.2 mg, 0.157 mmol) (Sigma-Aldrich, Saint Quentin Fallavier, France) was added as an internal standard for GC analysis. The reaction was triggered by the bubbling of the oxygen under the light of sodium lamp Faeber Lighting System 150W ST at 5 °C. The reaction was monitored by GC until the conversion of valencene into the hydroperoxides reached at least 95%. At the end of the reaction, the solvent was evaporated in vacuum. The NMR spectra showed the presence of hydroperoxide **2** as a major isomer with some hydroperoxide **3** (18%). The mixture was then left at room temperature under stirring for several hours. NMR spectra were recorded at *t* = 15 min and *t* = 48 h. The conversion of hydroperoxide **2** into hydroperoxide **4** was calculated using the olefinic signals.

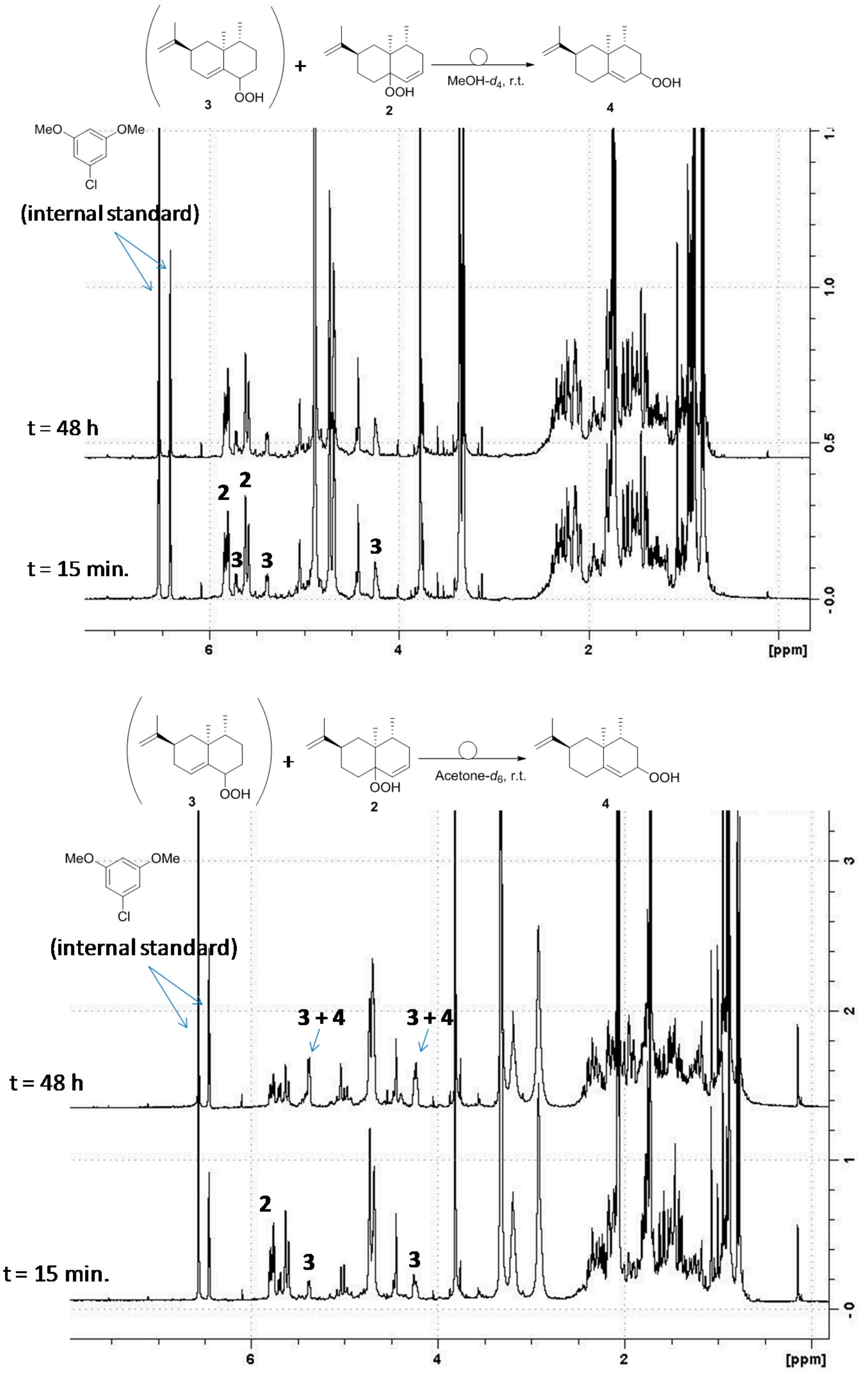


Figure S11. *Cont.*

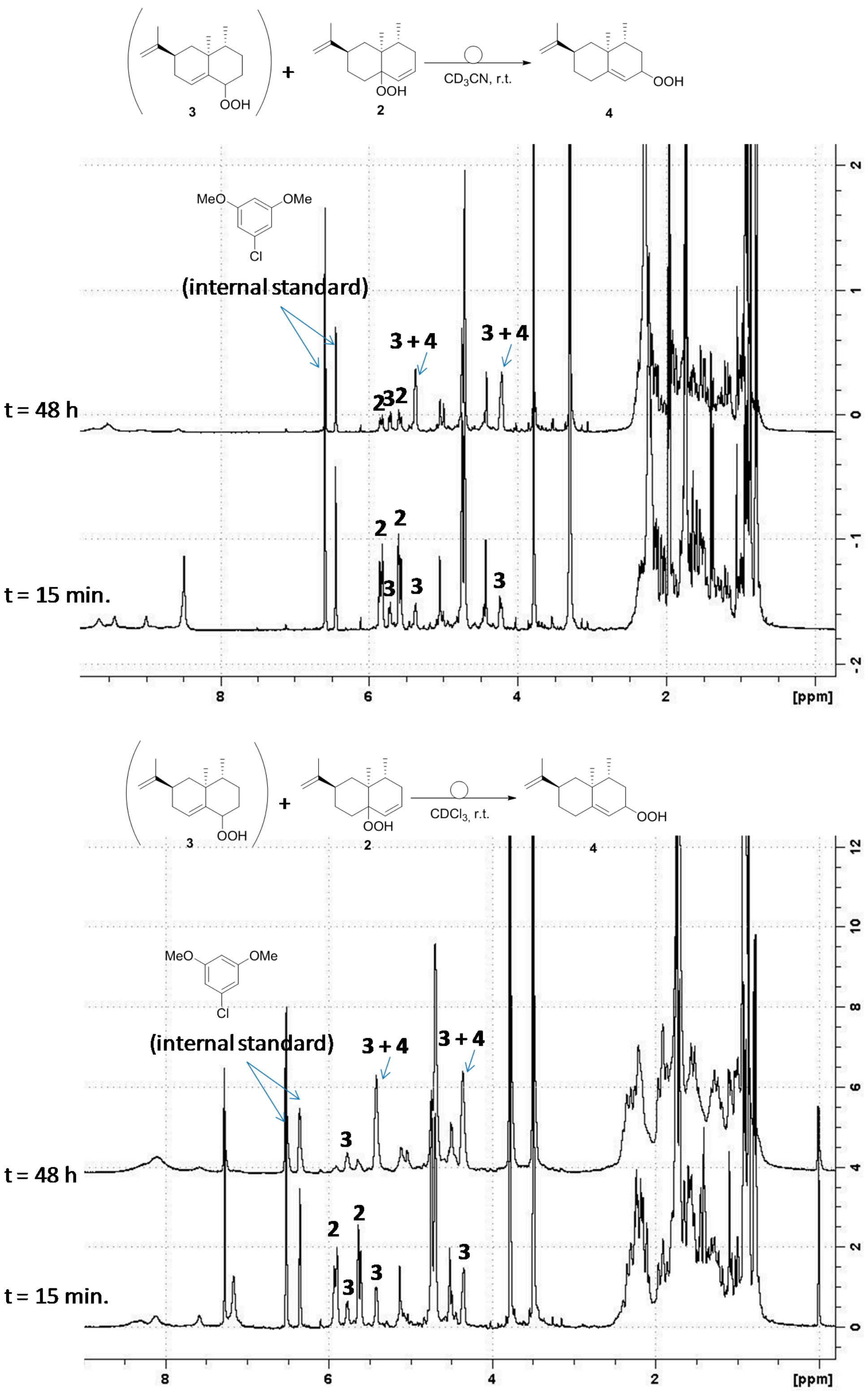


Figure S11. *Cont.*

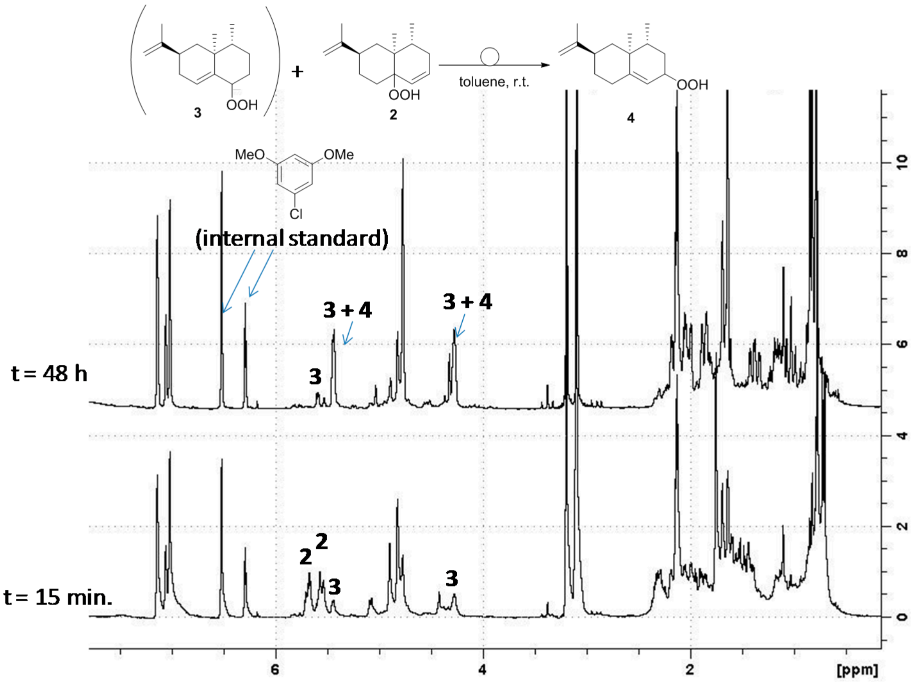
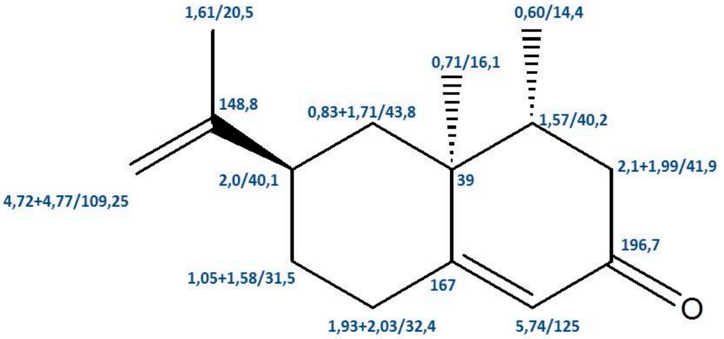
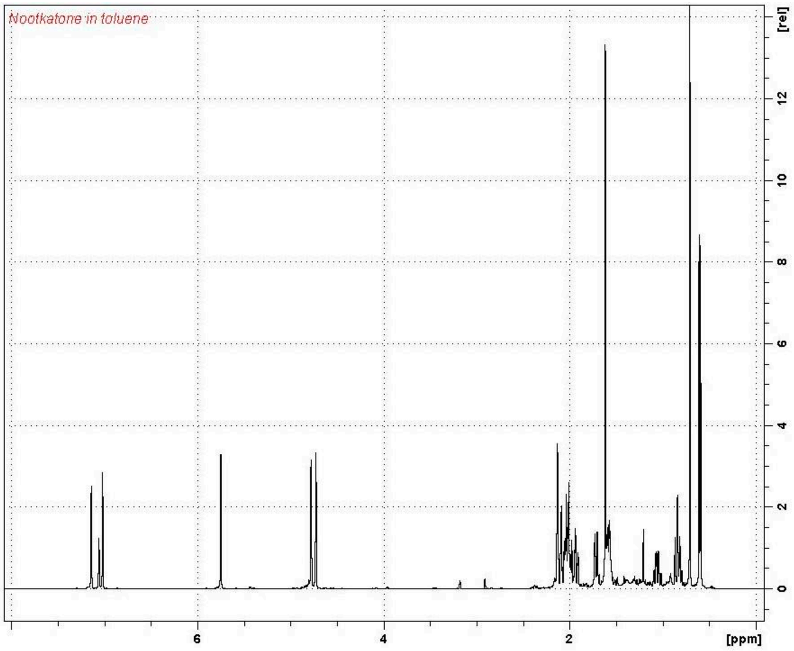
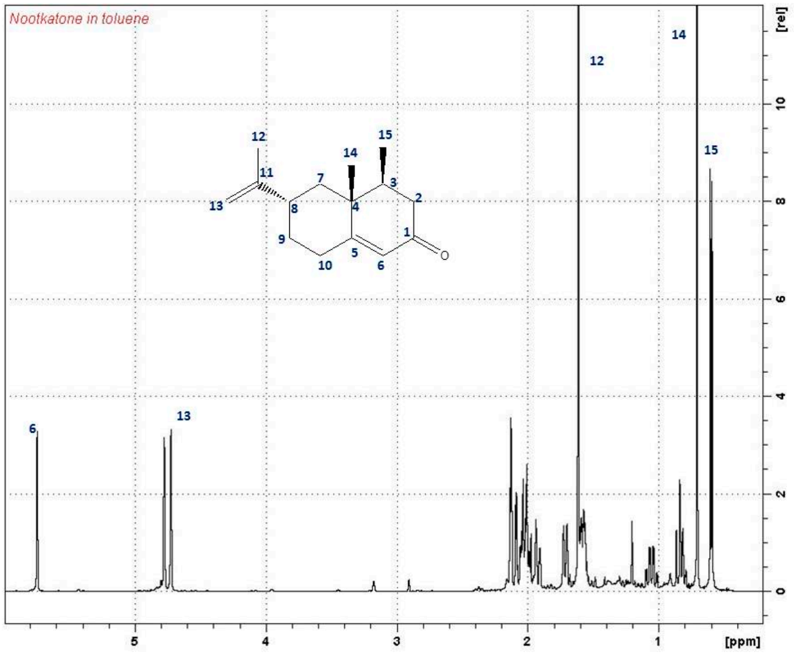


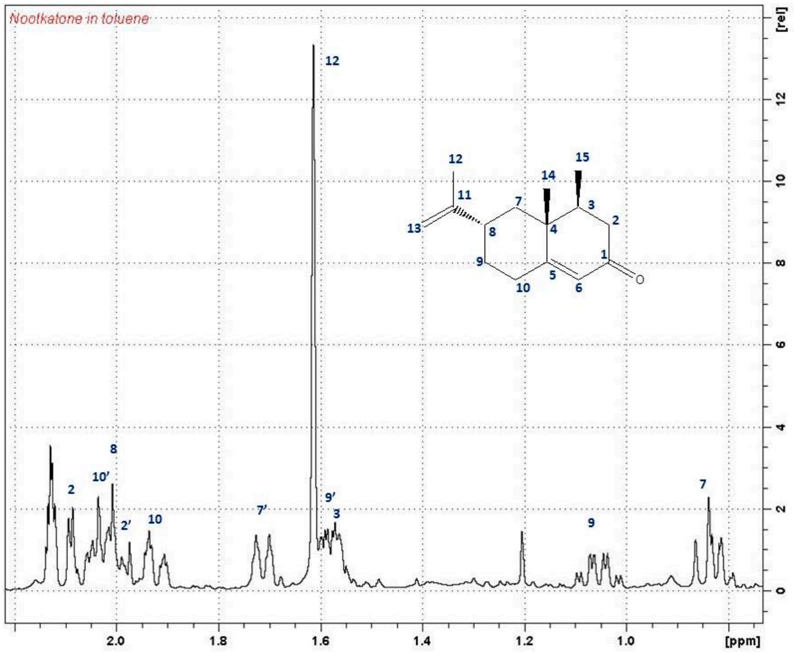
Figure S11. ^{1}H NMR spectra of hydroperoxides **2** and **3** at *t* = 15 min and *t* = 48 h in the different solvents.

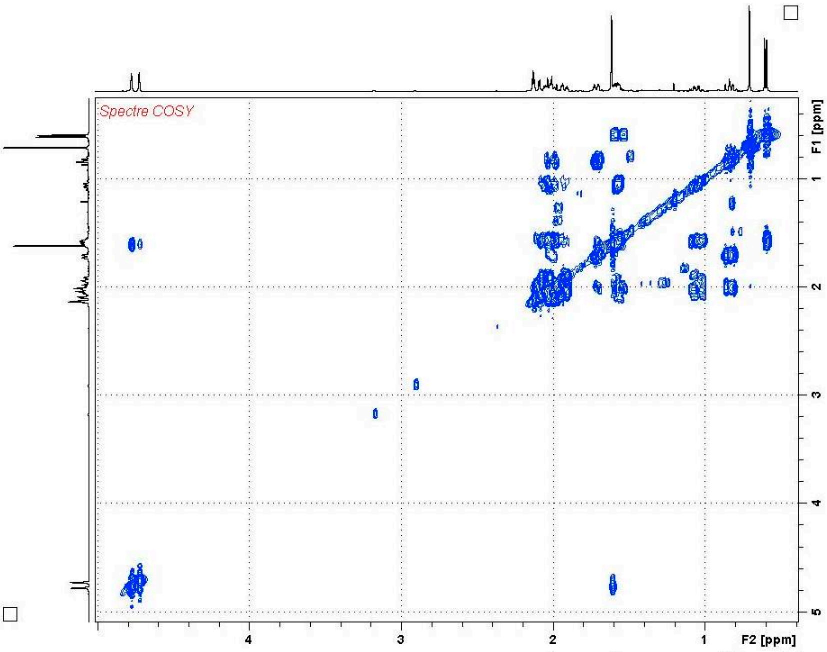
4. NMR Characterization of (+)-Nootkatone in Toluene-d8

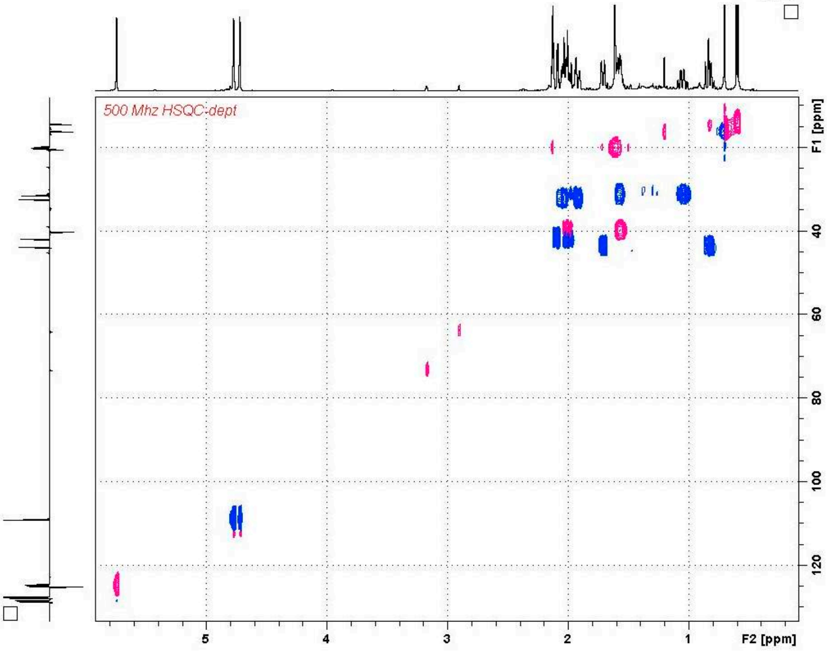


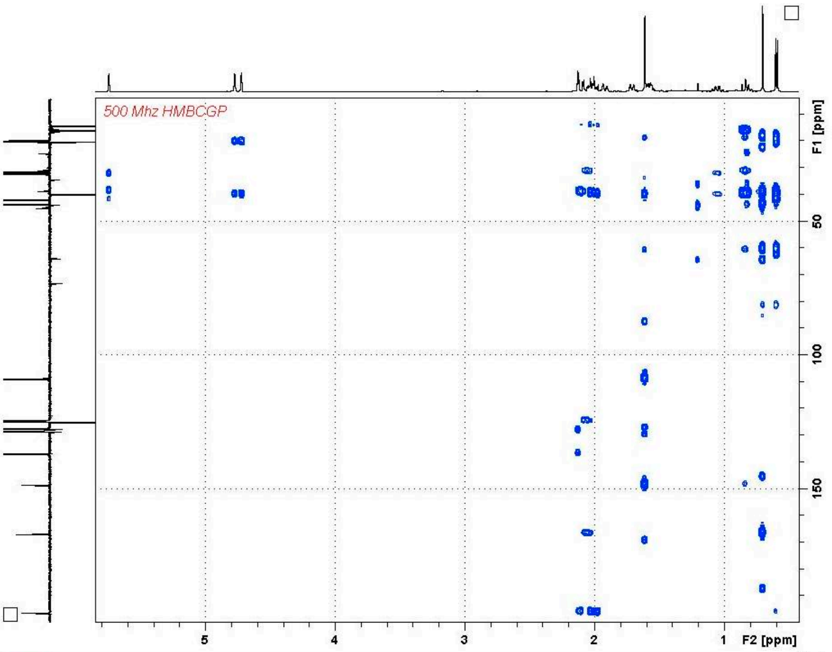


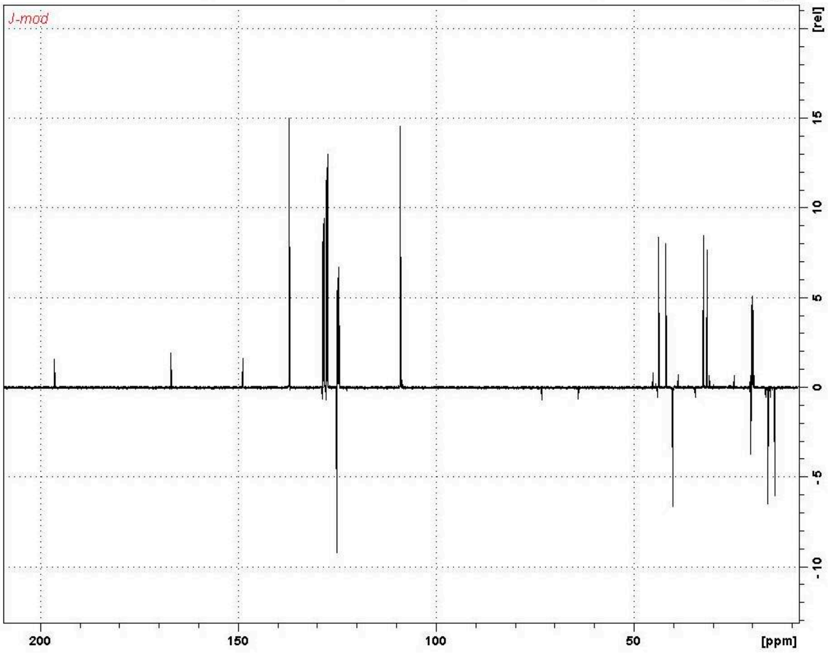

Nootkatone in toluene
12
14
15
6
13
12
11
13
8
7
14
4
15
3
2
1
9
10
5
6
[rel]
10
8
6
4
2
0
5
4
3
2
1
[ppm]

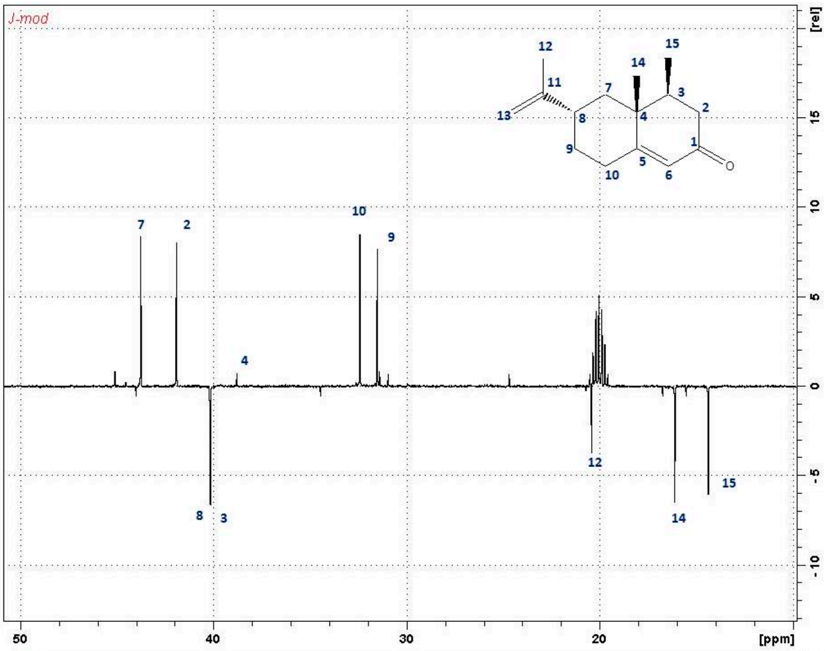

Nootkatone in toluene
12
12
11
13
8
7
14
4
15
3
2
1
9
10
5
6
2
10′
8
2′
10
7′
9′
3
9
7
[rel]
12
10
8
6
4
2
0
2.0
1.8
1.6
1.4
1.2
1.0
[ppm]

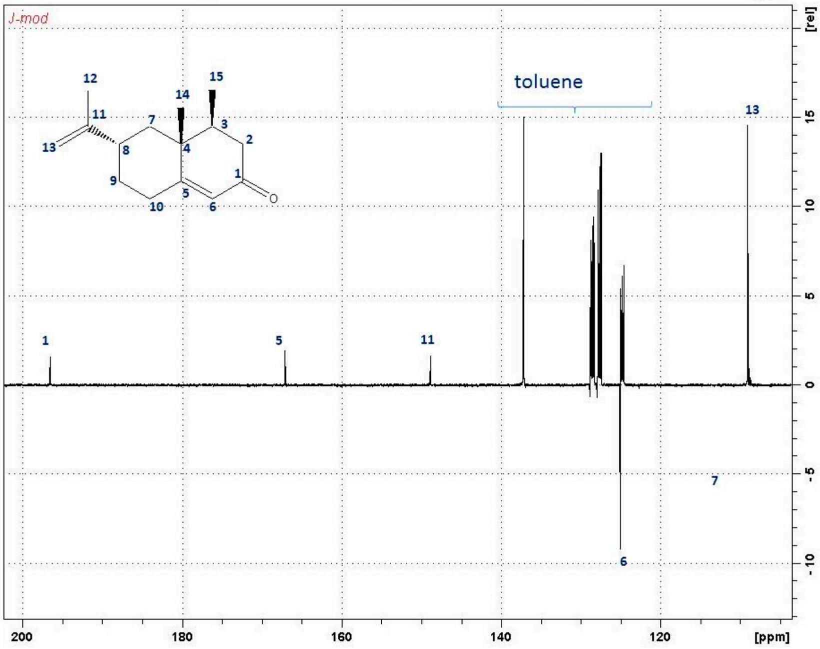

Spectre COSY
F1 [ppm]
1
2
3
4
5
F2 [ppm]
4
3
2
1


500 Mhz HSQC-dept
F1 [ppm]
20
40
60
80
100
120
F2 [ppm]
5
4
3
2
1


500 Mhz HMBCGP
F1 [ppm]
50
100
150
5
4
3
2
1
F2 [ppm]


J-mod
[rel]
15
10
5
0
-5
-10
200
150
100
50
[ppm]





5. Treatment of the Final Reaction Medium and Recycling

At the end of the reaction, the reaction medium formed a biphasic system (Figure S12, D) with an upper aqueous excess phase and a denser lower phase containing the catalyst and the product(s). An addition of 3 mL of diethyl ether yielded a Winsor II system (E): a lower aqueous colorless phase in equilibrium with a microemulsion phase containing the product, the catalyst, and some water. On the other hand, an addition of 6 mL diethyl ether gives the desired Winsor III system (Figure S13) with a water phase in excess, an oily phase in excess with the product(s) and a middle microemulsion phase with the catalyst (as indicated by the yellow color of this phase).

 **(A)**	 **(B)**	 **(C)**	 **(D)**	 **(E)**
t = 0 *valencene +* $C_8C_8MoO_4 + H_2O_2$	*valencene +* $C_8C_8MoO_4$ *after* H_2O_2 *consumption*	*valencene +* $C_8C_8MoO_4 + H_2O_2$ *(15th batch)*	*end of the reaction after decantation*	*end of the reaction with 3 mL of* Et_2O *WII system*

Figure S12. System evolution for valencene oxidation, using catalyst $C_8C_8MoO_4$ with several additions of H_2O_2, then diethyl ether for the recovery of the product.

Formation of a Winsor III system by addition of 6 mL diethyl ether:

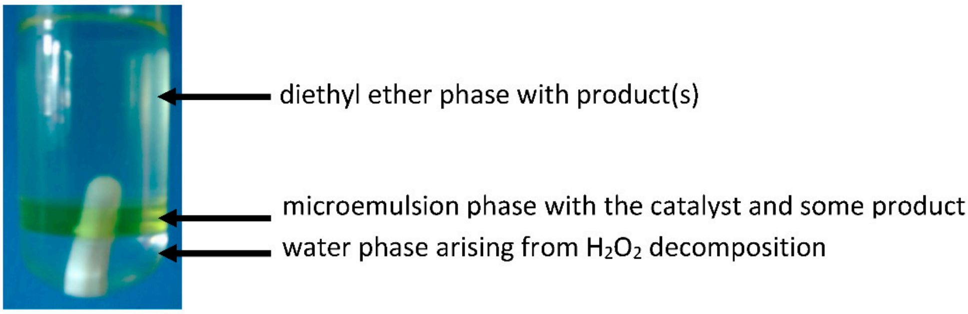


Figure S13. Winsor III microemulsion obtained by the addition of diethylether on the oxidation system of valencene with the catalyst $C_8C_8MoO_4$.

Separation of the organic phase and the removal of diethyl ether provided more than 80% of the product(s), which were also partitioned with the microemulsion phase. However, after two extractions with 6 mL of diethyl ether, all product(s) formed could be recovered. The combined organic phases, after solvent evaporation, provided (+)-nootkatone with a yield of 46.5%. The middle phase was charged again with starting valencene, and the reaction was conducted a second time. The system provided the same efficiency in terms of conversion and the formation of nootkatone. Kinetically, it appeared slightly superior, probably due to the preconditioning of the catalyst (the monoperoxide, which is formed from 1 equiv H_2O_2, does not decompose into singlet oxygen).