Supporting Information

Catalytic approach to *in vivo* metabolism of atractylenolide III using biomimetic iron-porphyrin complexes

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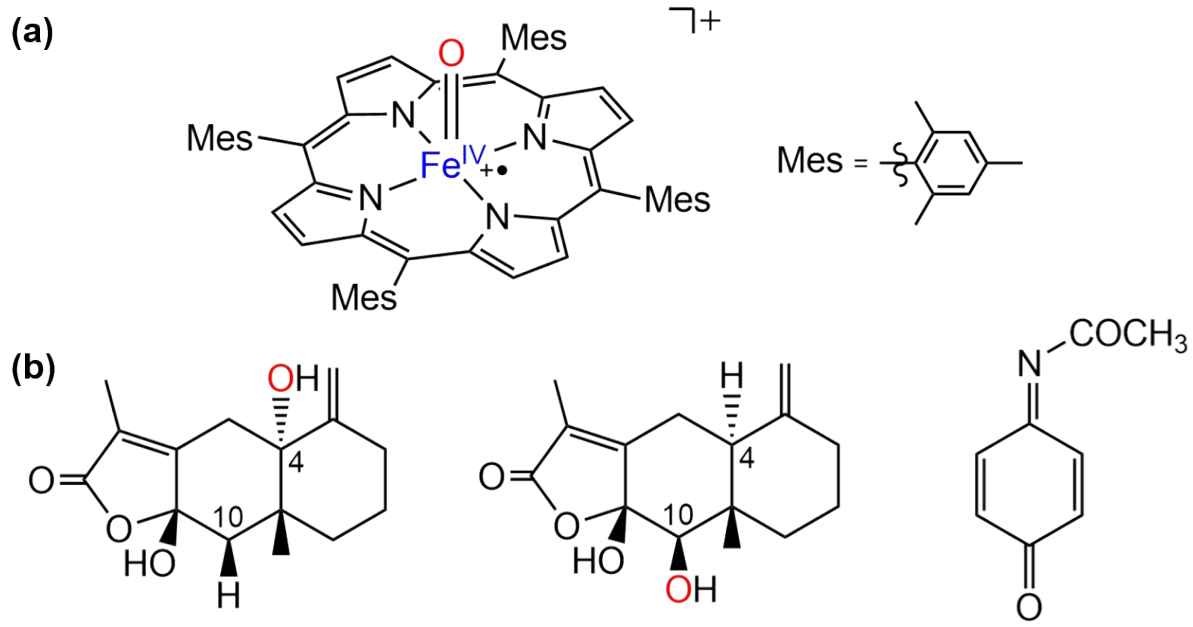

Scheme S1. (a) Structure of iron(IV)-oxo porphyrin π–cation radical complex (**1**) and (b) expected organic products obtained from the reaction between **1** and AT-III (left and middle) or APAP (right).

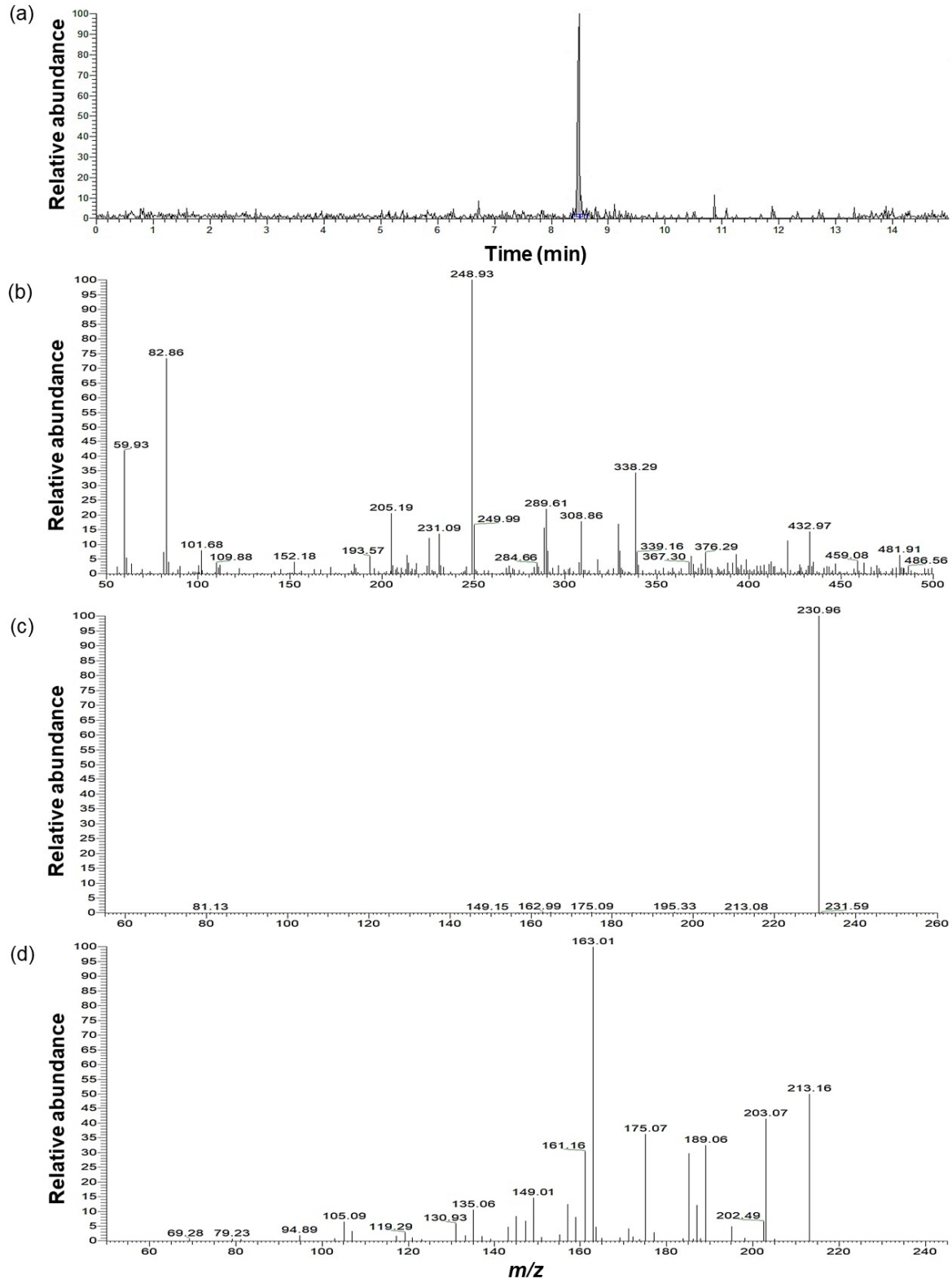

Fig. S1. (a) Chromatogram of atractylenolide III, and (b) the mass spectra of molecular ion observed at *m/z* 248.93 and the fragmented ions (c) at *m/z* 248.93 → 230.96 (MS^2) and (d) at *m/z* 230.96 → 213.16 (MS^3) in the plasma sample obtained 1 h after the oral administration of atractylenolide III.

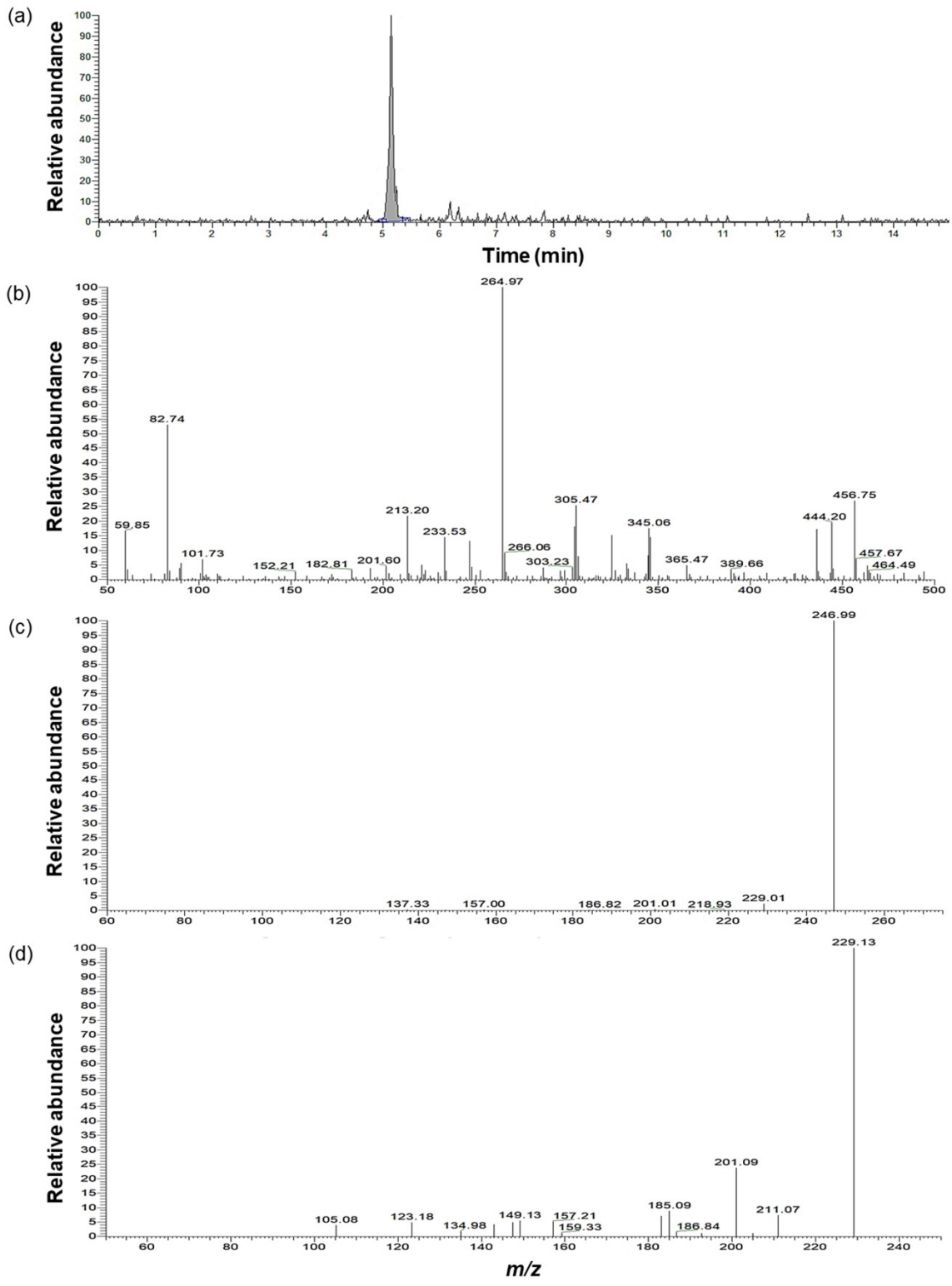

Fig. S2. (a) Chromatogram of the oxygenated atractylenolide III, (b) the mass spectra of the molecular ion at *m/z* 264.97, the fragmented ions at (c) *m/z* 264.97 → 246.99 (MS^2) and (d) at *m/z* 246.99 → 229.13 (MS^3) in the plasma sample obtained 1 h after the oral administration of atractylenolide III.

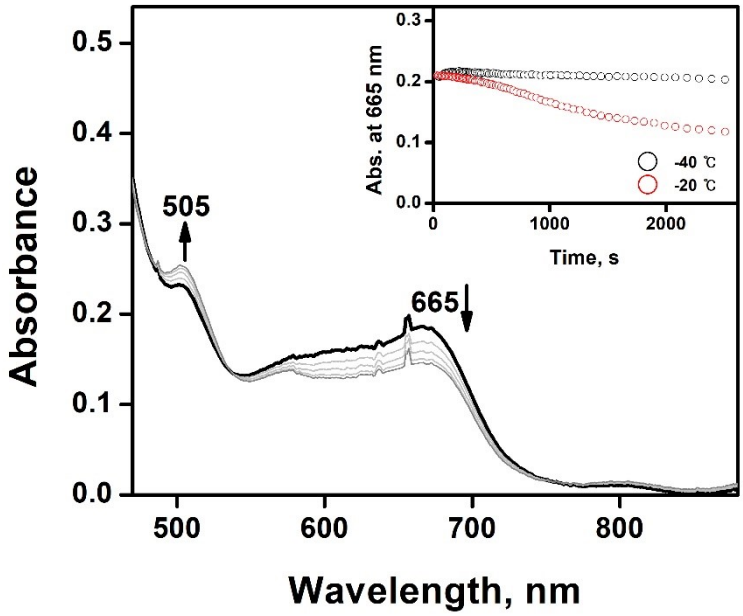

Fig. S3. UV-Vis spectral changes of **1** (0.025 mM) observed at –20 °C. The inset shows the time-courses that were monitored at 665 nm at –40 °C (black dot) and –20 °C (red dot) for the decay of **1**.

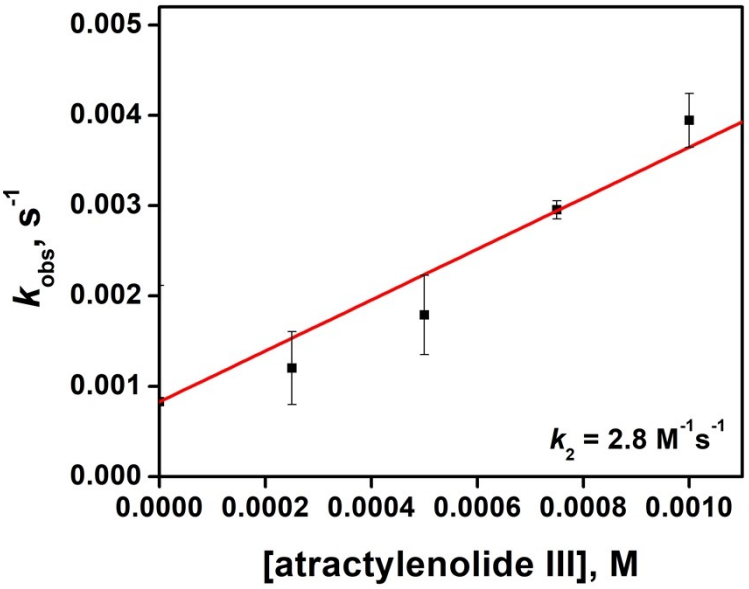

Fig. S4. Plot of pseudo-first order rate constants (k_{obs}) against the concentrations of AT-III to determine k_2 in the oxidation of AT-III by **1**.

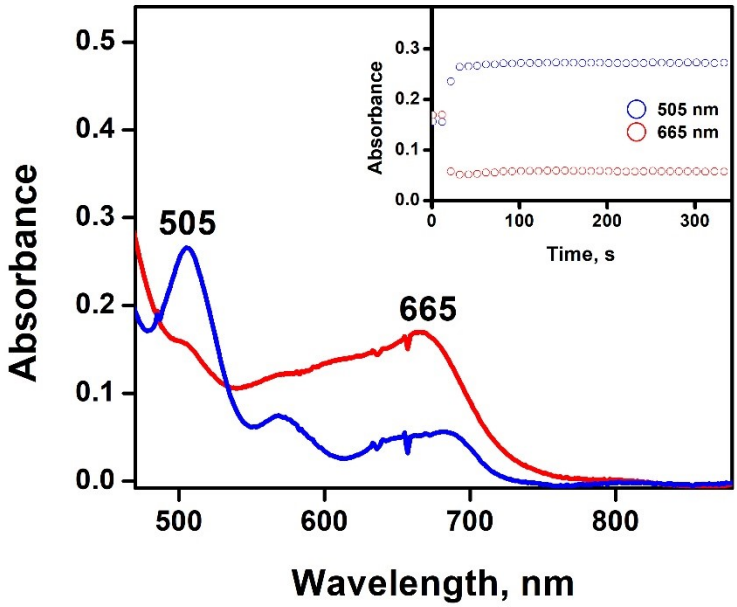

Fig. S5. UV-Vis spectral changes of $[(tmp^{+\bullet})Fe^{IV}(O)]^{+}$ (0.025 mM) (**1**, red line) after the addition of 20 equiv of APAP at –20 °C, resulting in the formation of $[Fe^{III}(tmp)](CF_3SO_3)$ (blue line). The inset shows the time-course of the formation of $[Fe^{III}(tmp)](CF_3SO_3)$ (blue dot) and the decay of **1** (red dot), which were monitored at 505 and 665 nm, respectively.

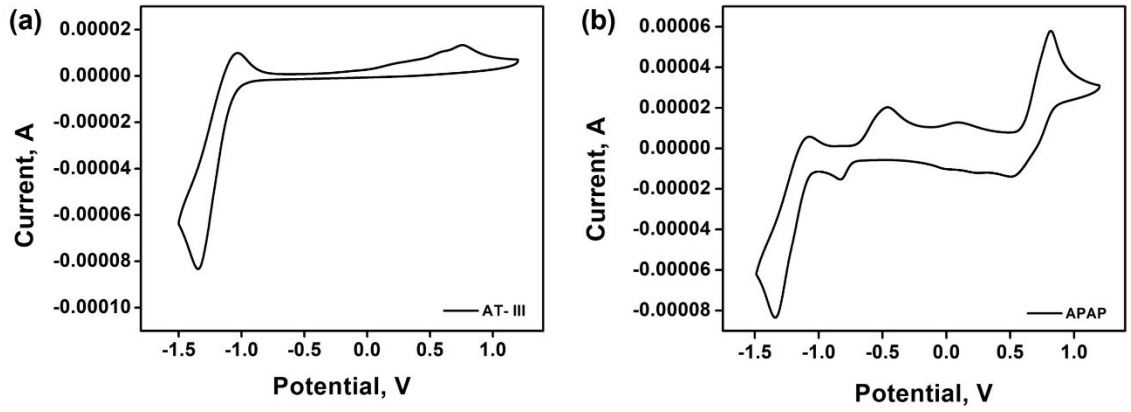

Fig. S6. Cyclic voltammograms of (a) AT-III (2.0 mM) and (b) APAP (2.0 mM) in deaerated CH_3CN containing $TBAPF_6$ (0.10 M) with a glassy carbon working electrode at 298 K. The scan rate was 0.10 V s^{-1}.

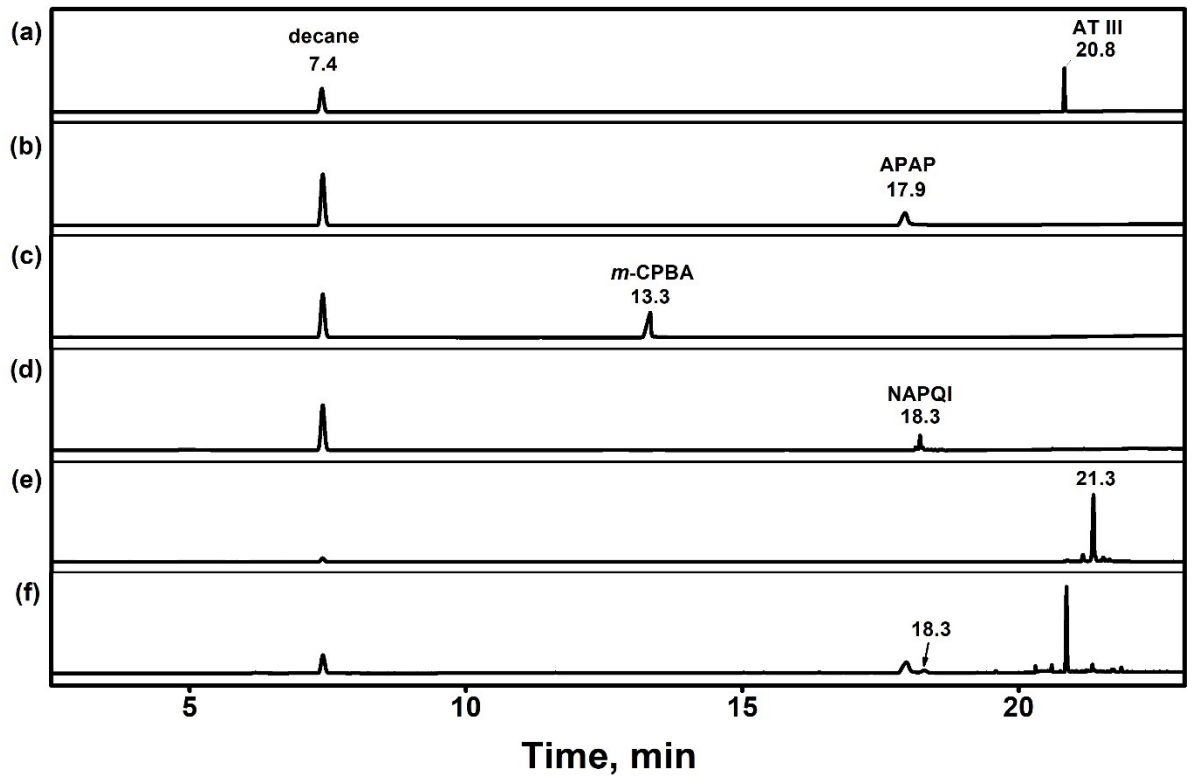

Fig. S7. GC data of the standard samples, namely, (a) AT-III, (b) APAP, (c) *m*-CPBA and (d) NAPQI as well as the products obtained from the oxygenation of AT-III by **1** in the (e) absence and (f) presence of APAP. The peak observed at 21.3 min corresponded to the oxygenated product of AT-III.

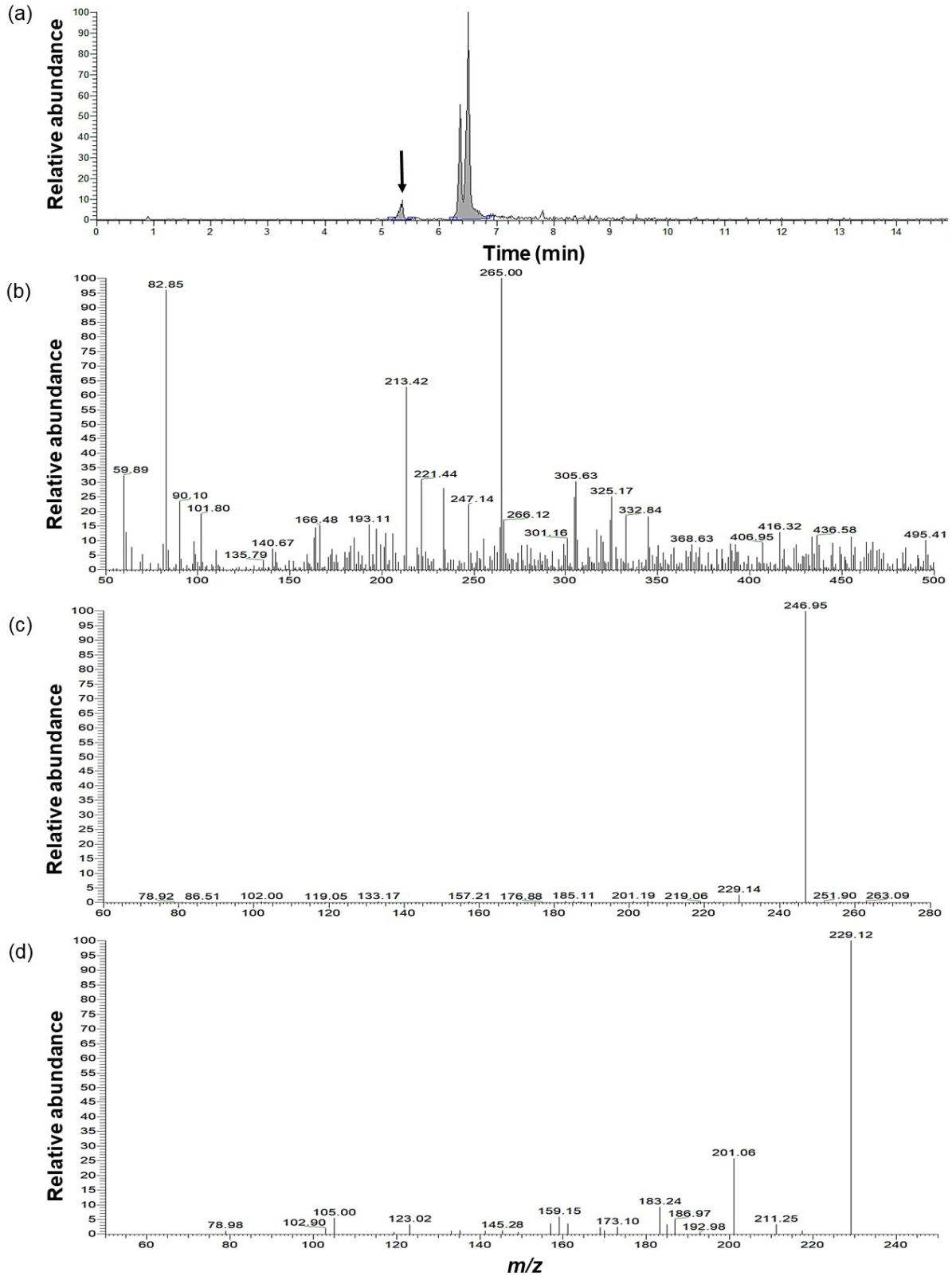

Fig. S8. (a) Chromatogram of oxygenated atractylenolide III, (b) the mass spectra of molecular ion at *m/z* 265.00, (c) the fragmented ions at *m/z* 265.00 → 246.95 (MS^2) and (d) at *m/z* 246.95 → 229.12 (MS^3) derived from the oxidation of atractylenolide III reacted with $[(tmp^{+\bullet})Fe^{IV}(O)]^+$ (**1**). The black arrow in (a) indicates the oxygenated atractylenolide III, which matches that observed in the plasma samples.

Coordinates

The coordinates are provided in .xyz-format, with charge/multiplicity in parenthesis in the comment row.

AT-III
```
38
(0/1)
C -3.36063 -0.89539 0.79099
C -3.26642 0.62031 1.03813
C -2.50649 1.31495 -0.06967
C -1.13626 0.73487 -0.38024
C -1.21307 -0.81227 -0.64247
C -1.98315 -1.50938 0.51104
C -0.11520 1.11937 0.73750
C 1.20762 0.50642 0.44077
C 1.23030 -0.99794 0.25232
C 0.21212 -1.41129 -0.80892
C 2.42498 1.01199 0.17697
C 3.30457 -0.12728 -0.22654
O 2.56731 -1.28290 -0.18328
C -3.00167 2.36258 -0.74268
C -1.94831 -1.05299 -1.97719
O 0.96984 -1.70240 1.43298
C 2.94711 2.40994 0.19497
O 4.45713 -0.10149 -0.55919
H -4.04523 -1.08260 -0.05303
H -3.81332 -1.38827 1.66744
H -4.26804 1.06441 1.14852
H -2.74425 0.78725 1.99928
H -0.76607 1.20501 -1.30709
H -2.09132 -2.57944 0.26415
H -1.37535 -1.47957 1.42729
H -0.04992 2.21491 0.80977
H -0.47208 0.74796 1.71262
H 0.62572 -1.08271 -1.77505
H 0.16246 -2.51191 -0.83392
H -3.98674 2.77803 -0.50903
H -2.43959 2.84290 -1.54968
H -2.01470 -2.13174 -2.19300
H -1.41085 -0.57704 -2.81337
H -2.96853 -0.64460 -1.97133
H 1.62330 -1.43443 2.09601
H 3.34557 2.68686 -0.79478
H 2.17274 3.13603 0.48012
H 3.78895 2.49991 0.90111
```

One electron oxidized AT-III
```
38
(1/2)
C -3.00112 -0.62191 1.50217
C -3.42705 0.73487 0.99411
C -2.81976 0.99723 -0.40098
C -1.29064 0.84296 -0.70925
C -1.22485 -0.65115 -0.18445
C -1.51415 -0.82053 1.31869
C -0.05149 1.20462 0.13728
C 1.23497 0.39119 0.12020
C 1.39800 -1.18117 0.27273
C 0.12255 -1.32510 -0.57773
C 2.35154 1.10094 0.07645
C 3.43637 0.15556 0.09554
O 2.86951 -1.12075 -0.03514
C -3.63455 1.44126 -1.38867
C -2.28489 -1.42145 -0.99358
O 1.62359 -2.39797 -0.44367
C 2.46667 2.63582 0.02790
O 4.66108 0.42333 0.20546
H -3.49447 -1.37171 0.91952
H -3.27730 -0.72534 2.53075
H -4.49605 0.73609 0.94790
H -3.09453 1.51448 1.64719
H -1.33660 1.87388 -0.42626
H -1.27885 -1.81716 1.62889
H -0.93055 -0.12901 1.88960
H 0.20937 2.19103 -0.18494
H -0.36189 1.19989 1.16117
H 0.33751 -0.97704 -1.56645
H -0.05983 -2.37944 -0.56862
H -4.67867 1.57924 -1.19937
H -3.23392 1.65392 -2.35771
H -2.25984 -2.04775 -0.12642
H -1.66693 -1.20399 -1.83964
H -2.44336 -2.37899 -1.44400
H 0.78282 -2.82779 -0.61709
H 3.35707 2.91021 -0.49828
H 1.61482 3.04168 -0.47669
H 2.50819 3.02205 1.02491
```

4th carbon oxidized AT-III
```
39
(0/1)
C -3.27200 -1.12755 0.83091
C -3.20856 0.35461 1.22531
C -2.49111 1.19430 0.19142
C -1.10926 0.69428 -0.24455
C -1.16999 -0.84278 -0.64026
C -1.88075 -1.65775 0.47301
C -0.08819 0.95909 0.90555
C 1.24028 0.39472 0.54820
C 1.28556 -1.07365 0.19648
C 0.26558 -1.37981 -0.90583
C 2.45221 0.93595 0.35085
C 3.34960 -0.14243 -0.16203
O 2.61262 -1.29558 -0.28729
C -3.01332 2.32645 -0.29975
C -1.95566 -1.00441 -1.96016
O 1.09039 -1.82228 1.36559
C 2.95245 2.33122 0.51662
O 4.50810 -0.07711 -0.46527
H -3.96651 -1.25416 -0.01610
H -3.69152 -1.71754 1.66250
H -4.21669 0.76104 1.40088
H -2.67092 0.43657 2.18868
H -1.95155 -2.70860 0.14119
H -1.25391 -1.67009 1.37622
H -0.04202 2.04485 1.06692
H -0.44334 0.49009 1.83595
H 0.65070 -0.91885 -1.82634
H 0.22981 -2.46989 -1.08203
H -3.99774 2.67845 0.02171
H -2.46802 2.94793 -1.01315
H -2.06397 -2.07251 -2.20741
H -1.42833 -0.53610 -2.80589
H -2.96491 -0.57067 -1.90655
H 1.12485 -2.76045 1.12825
H 3.33960 2.71814 -0.44011
H 2.16672 3.00962 0.87703
H 3.79497 2.35749 1.22702
O -0.59340 1.45093 -1.32908
H -1.23002 1.41372 -2.05496
```

10th carbon oxidized AT-III
```
39
(0/1)
C 3.36993 0.66955 0.89940
C 3.28904 -0.86383 0.99837
C 2.52043 -1.45405 -0.16265
C 1.14435 -0.85261 -0.40174
C 1.22258 0.70770 -0.52921
C 1.98736 1.29936 0.68426
C 0.14390 -1.32643 0.69795
C -1.18509 -0.71166 0.44415
C -1.24001 0.79751 0.35605
C -0.21263 1.33331 -0.66305
C -2.39048 -1.22087 0.13224
C -3.29260 -0.07534 -0.18759
O -2.57562 1.09076 -0.05232
C 3.01097 -2.43079 -0.93749
C 1.95505 1.07328 -1.83680
O -0.98723 1.45111 1.57494
C -2.88164 -2.62702 0.04410
O -4.44358 -0.09359 -0.52173
H 4.04914 0.94452 0.07588
H 3.82190 1.07862 1.81834
H 4.29481 -1.30877 1.05383
H 2.77974 -1.12825 1.94451
H 0.75998 -1.24544 -1.35825
H 2.08818 2.38587 0.53681
H 1.38858 1.17210 1.59931
H 0.09043 -2.42481 0.69801
H 0.50323 -1.01497 1.69261
H -0.60412 1.03487 -1.65016
H 4.00078 -2.86090 -0.75636
H 2.44126 -2.83498 -1.78002
H 1.96144 2.16520 -1.96866
H 1.44282 0.63141 -2.70717
H 2.99176 0.71047 -1.85099
H -1.73033 1.28247 2.17247
H -3.27243 -2.83735 -0.96485
H -2.09195 -3.35519 0.27651
H -3.72209 -2.78771 0.73924
O -0.18595 2.73709 -0.63686
H -0.30113 3.00106 0.28882
```

Radical on 4th carbon of AT-III
```
37
(0/1)
C 3.69030 -0.93120 0.60740
C 3.80720 0.28160 -0.32620
C 2.54110 1.14240 -0.35750
C 1.28660 0.57320 -0.04240
C 1.12400 -0.84950 0.51070
C 2.40370 -1.69920 0.28220
C 0.03490 1.44730 -0.07320
C -1.21550 0.63630 -0.12240
C -1.11580 -0.69980 -0.81460
C -0.09040 -1.61790 -0.14440
C -2.46140 0.84010 0.34970
C -3.28520 -0.34050 0.00110
O -2.48360 -1.27340 -0.67600
C 2.69340 2.47810 -0.71420
C 0.84540 -0.73300 2.04540
O -0.84720 -0.45580 -2.19170
C -3.03790 1.99620 1.10080
O -4.47330 -0.56880 0.24210
H 3.69030 -0.60380 1.65530
H 4.56150 -1.58550 0.48220
H 4.66080 0.90740 -0.04100
H 4.01530 -0.07800 -1.34580
H 2.32860 -2.61830 0.87770
H 2.44280 -2.00630 -0.77280
H 0.00920 2.14220 0.77940
H 0.06090 2.08150 -0.97150
H -0.60310 -2.20010 0.62610
H 0.27560 -2.33160 -0.89250
H 3.67700 2.87740 -0.93990
H 1.86600 3.17420 -0.78460
H 0.74950 -1.73390 2.48350
H -0.08370 -0.18780 2.24220
H 1.65900 -0.20820 2.55520
H -0.60270 -1.28730 -2.64910
H -3.57830 1.65340 1.99040
H -2.25990 2.69640 1.41540
H -3.75650 2.54730 0.48130
```

Radical on 10th carbon of AT-III
```
37
(0/1)
C 3.43250 -0.90790 -0.66900
C 3.30620 0.59590 -1.00230
C 2.49120 1.31860 0.05200
C 1.11780 0.73150 0.34920
C 1.19810 -0.81780 0.66530
C 2.05030 -1.54760 -0.44050
C 0.11030 1.06590 -0.81120
C -1.21120 0.46090 -0.49030
C -1.22550 -1.04070 -0.27190
C -0.18130 -1.43560 0.70680
C -2.41460 0.99720 -0.19100
C -3.30340 -0.08970 0.27610
O -2.59460 -1.30330 0.25380
C 2.94470 2.40330 0.70030
C 1.85850 -1.01190 2.05430
O -1.05910 -1.80400 -1.48260
C -2.88280 2.41570 -0.23070
O -4.47220 -0.03770 0.66740
H 4.06490 -1.03330 0.21900
H 3.93940 -1.42790 -1.49180
H 4.29680 1.05540 -1.09390
H 2.81950 0.69380 -1.98530
H 0.72050 1.21890 1.24930
H 2.16320 -2.59880 -0.14630
H 1.48660 -1.54600 -1.38060
H 0.04070 2.15200 -0.91910
H 0.48700 0.66390 -1.76020
H -0.38110 -2.28270 1.35560
H 3.92060 2.83040 0.48470
H 2.35560 2.90300 1.46510
H 1.96130 -2.07910 2.28280
H 1.24500 -0.55230 2.83760
H 2.85110 -0.55510 2.09350
H -1.66200 -1.47020 -2.18360
H -3.21830 2.74550 0.75980
H -2.09150 3.08940 -0.56720
H -3.73650 2.52580 -0.91040
```