Supplementary Material (ESI) for Organic & Biomolecular Chemistry

ELECTRONIC SUPPLEMENTARY INFORMATION

An important role of intramolecular free radical reactions in antimalarial activity of artemisinin and its analogs

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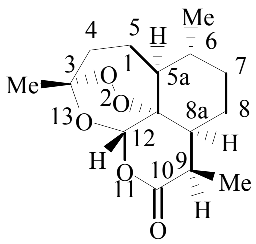

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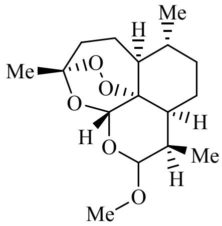

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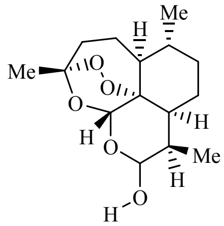

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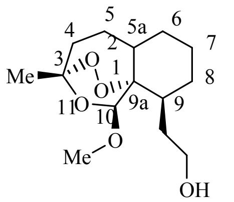

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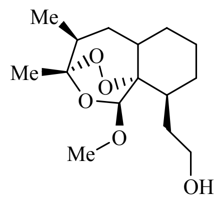

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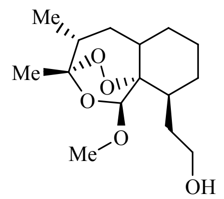

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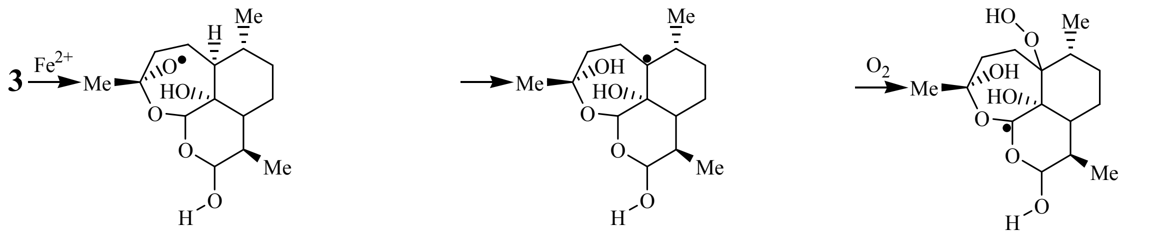

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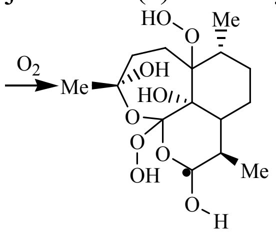
Supplementary Material (ESI) for Organic & Biomolecular Chemistry



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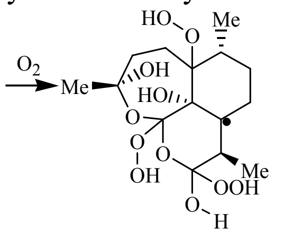

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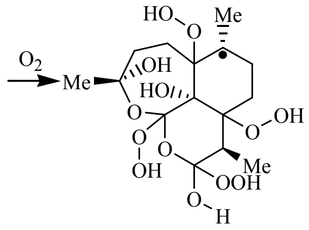

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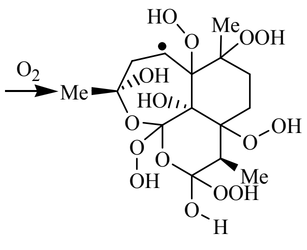

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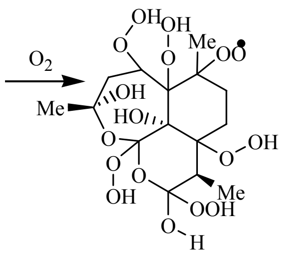

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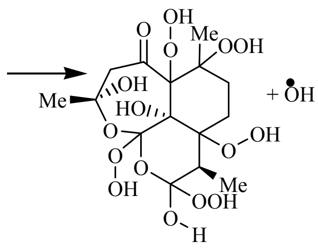

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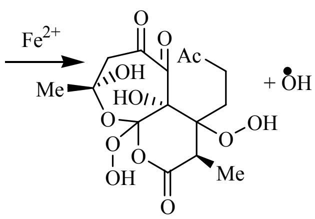

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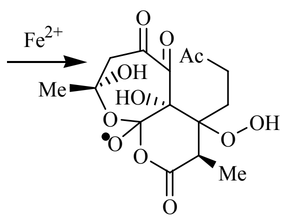

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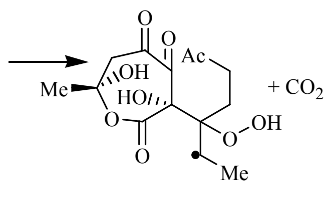

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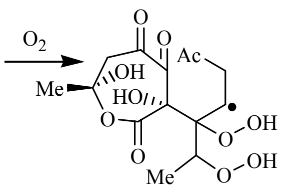

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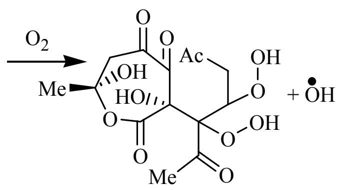

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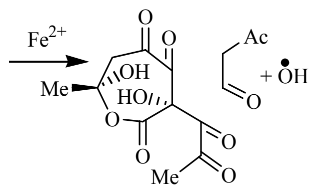

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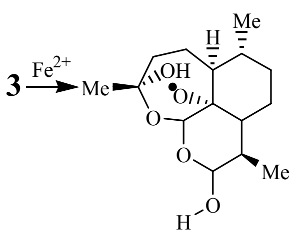

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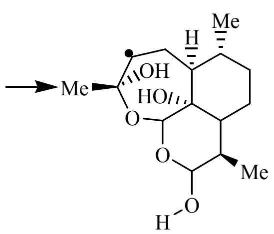

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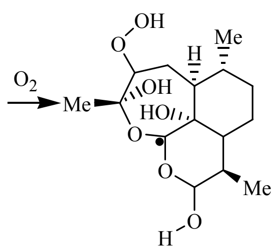

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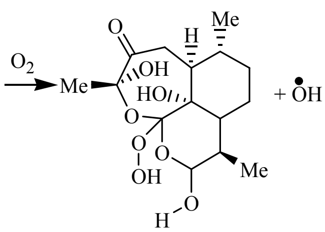

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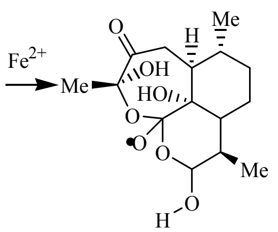

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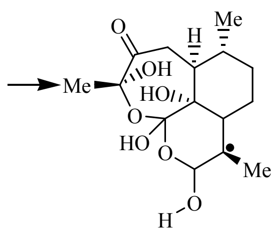

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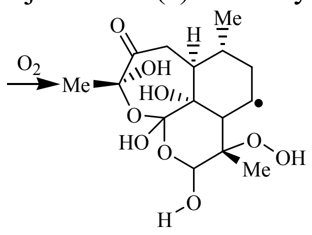

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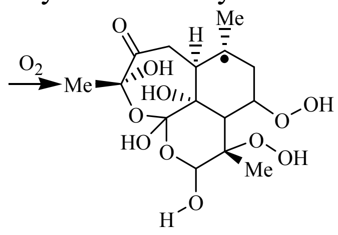

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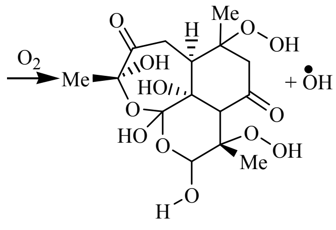

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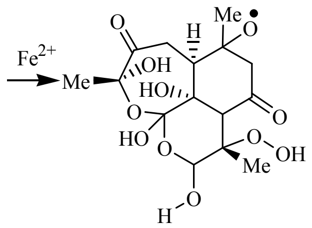

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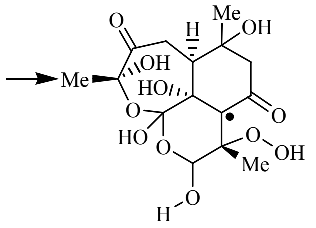

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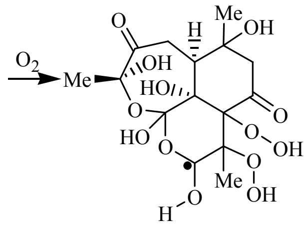

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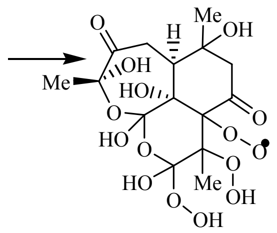

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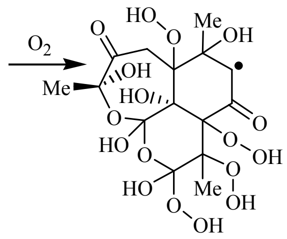

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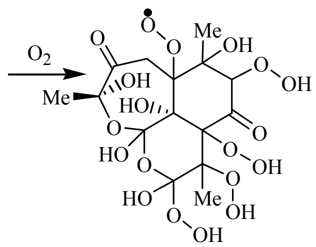

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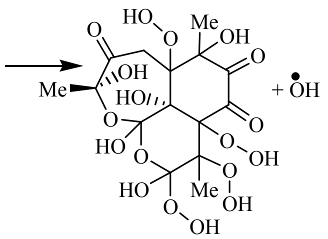

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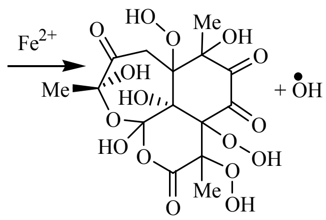

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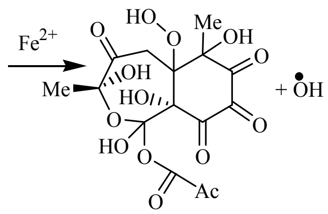

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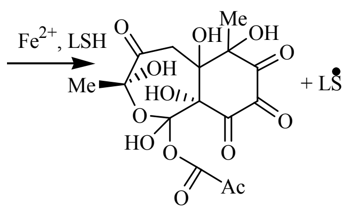

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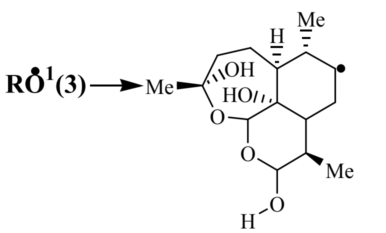

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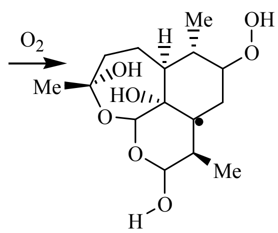

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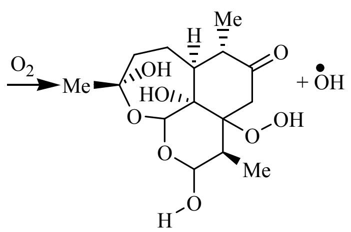

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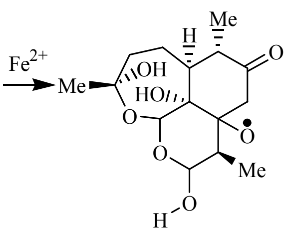

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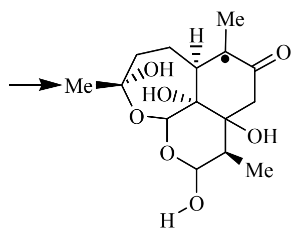

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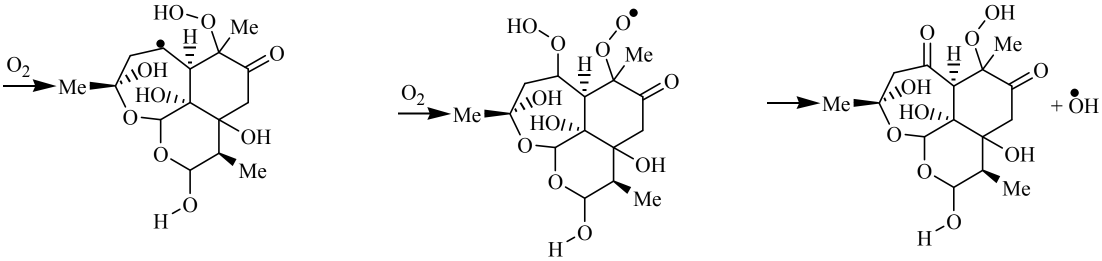

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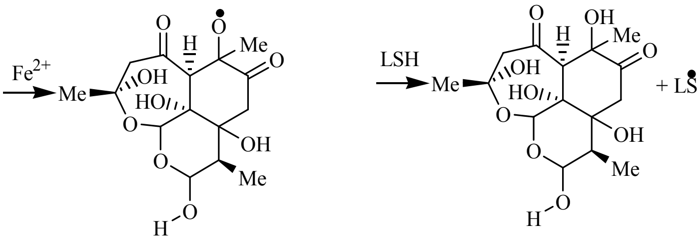
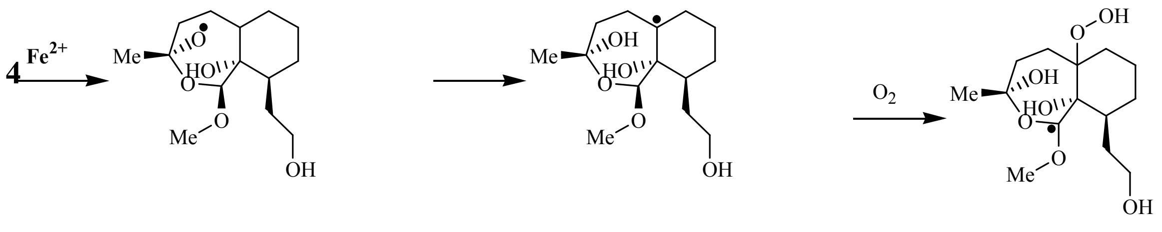


90 **91**

Scheme 2. Stages of the intramolecular oxidation of compound **3.** Kinetic characteristics (ΔH, E, k) of elementary steps of intramolecular oxidation of compound **3** are given in Table 6.

As in the case of compound **2**, free radical $RO^{1\bullet}$(**3**) is isomerized in parallel to alkyl radicals $R^{4\bullet}$(**3**) and $R^{7\bullet}$(**3**) with the ratio of rate constants 2:1. The oxidation and destruction of $R^{4\bullet}$(**3**) produces three hydroxy radicals and one thiyl radical, and the oxidation of $R^{7\bullet}$(**3**) produces two hydroxy radicals and one $LS^{\bullet}$ radical. Radical $RO^{2\bullet}$ is generated due to the oxidation of six hydroxy radicals. The total yield of radicals per molecule of **3** is equal to 4.33 hydroxy radicals (that is more than **1 !**) and 0.5 $LS^{\bullet}$ radical.



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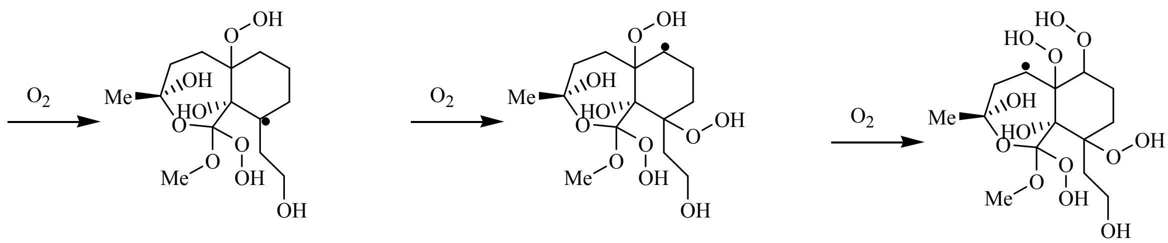

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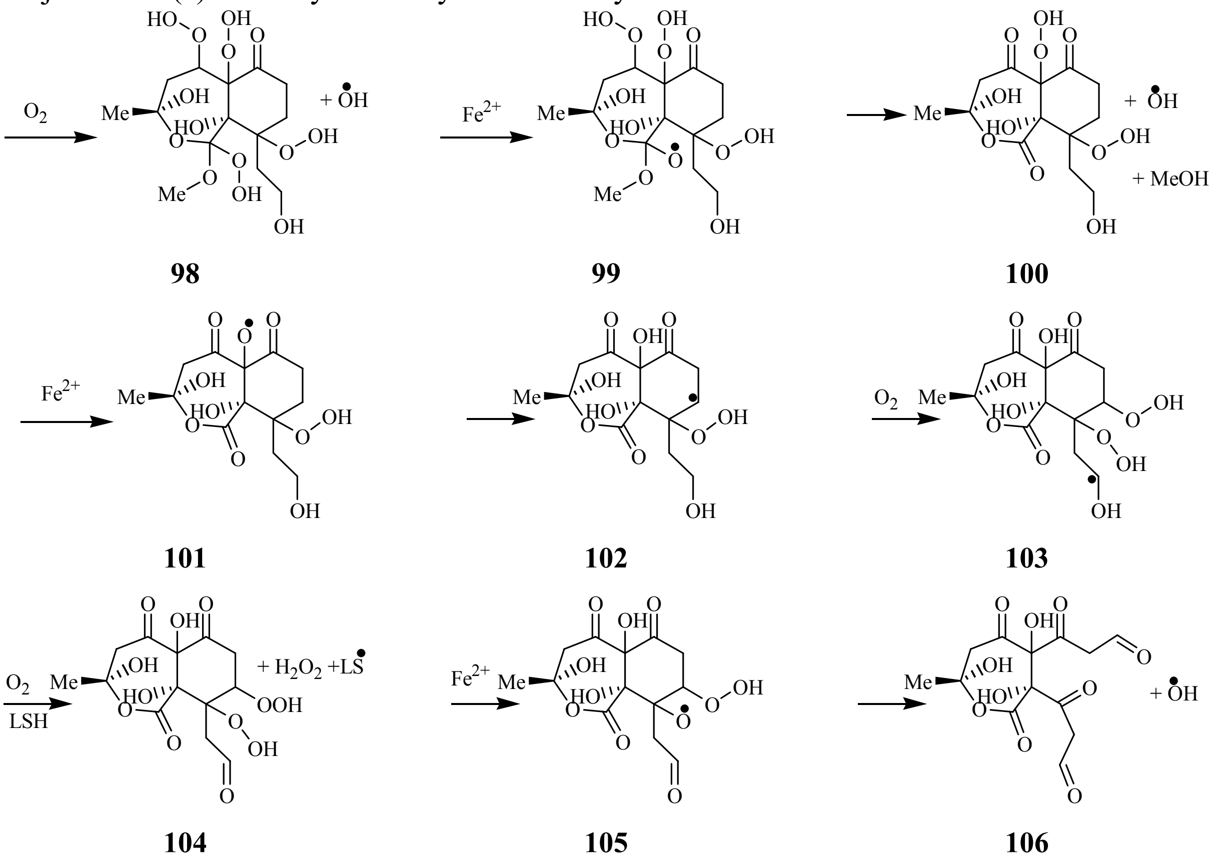
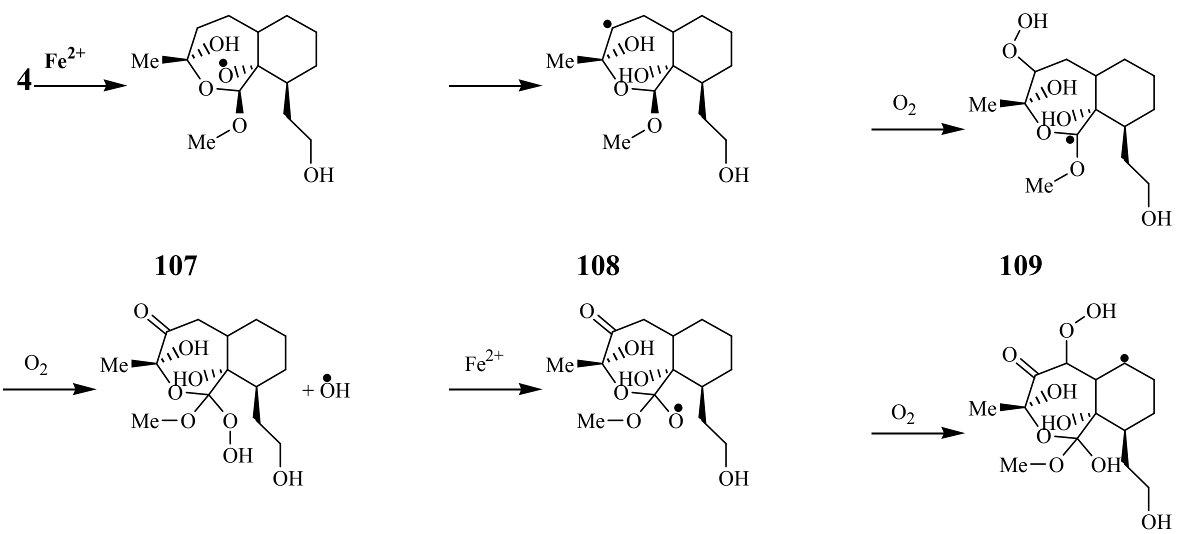


Scheme 3. Stages of the intramolecular oxidation of radical RO$^{2\bullet}$ of compound **4.** Kinetic characteristics (Δ*H, E, k*) of elementary steps of the intramolecular oxidation of compound **4** are given in Table 6.

It is seen that the intramolecular oxidation of radical RO$^{2\bullet}$(**4**) proceeds *via* a line of consecutive reactions and generates, as a result, three HO$^{\bullet}$ radicals and one LS$^{\bullet}$ radical. The same cascade of free radical reactions proceeds in the case of intramolecular transformations of radicals RO$^{2\bullet}$**(5)** and RO$^{2\bullet}$**(6)**.



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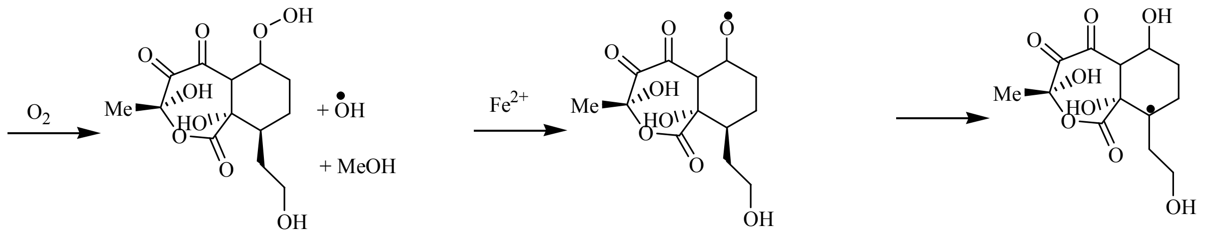

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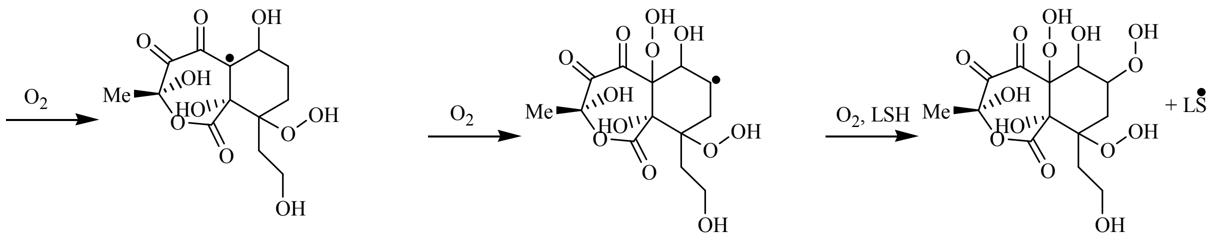

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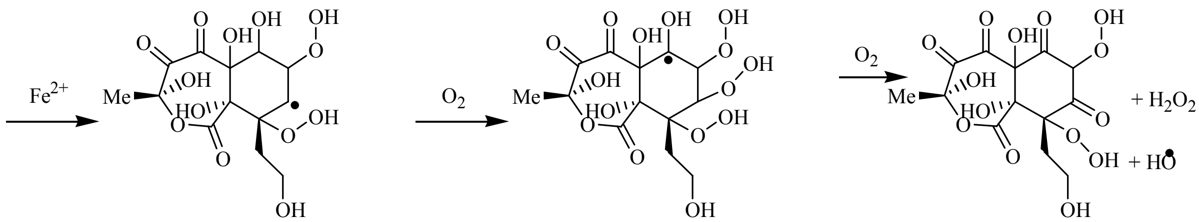

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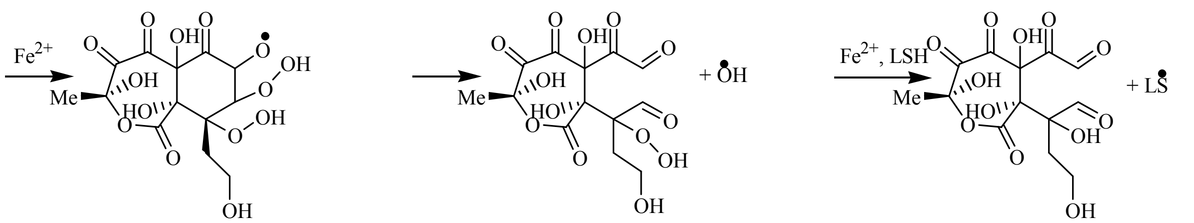

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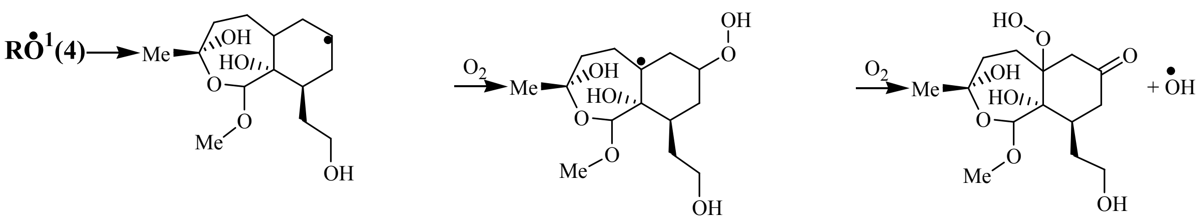

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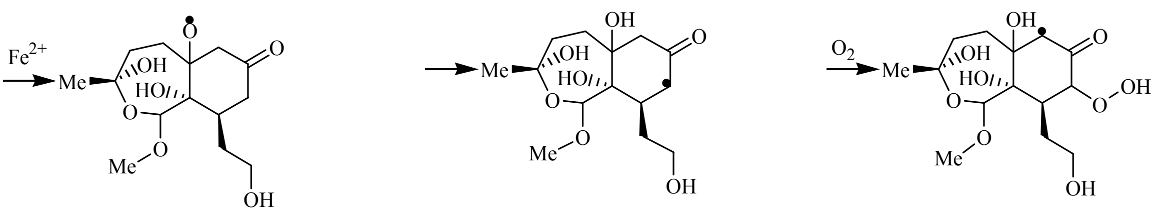

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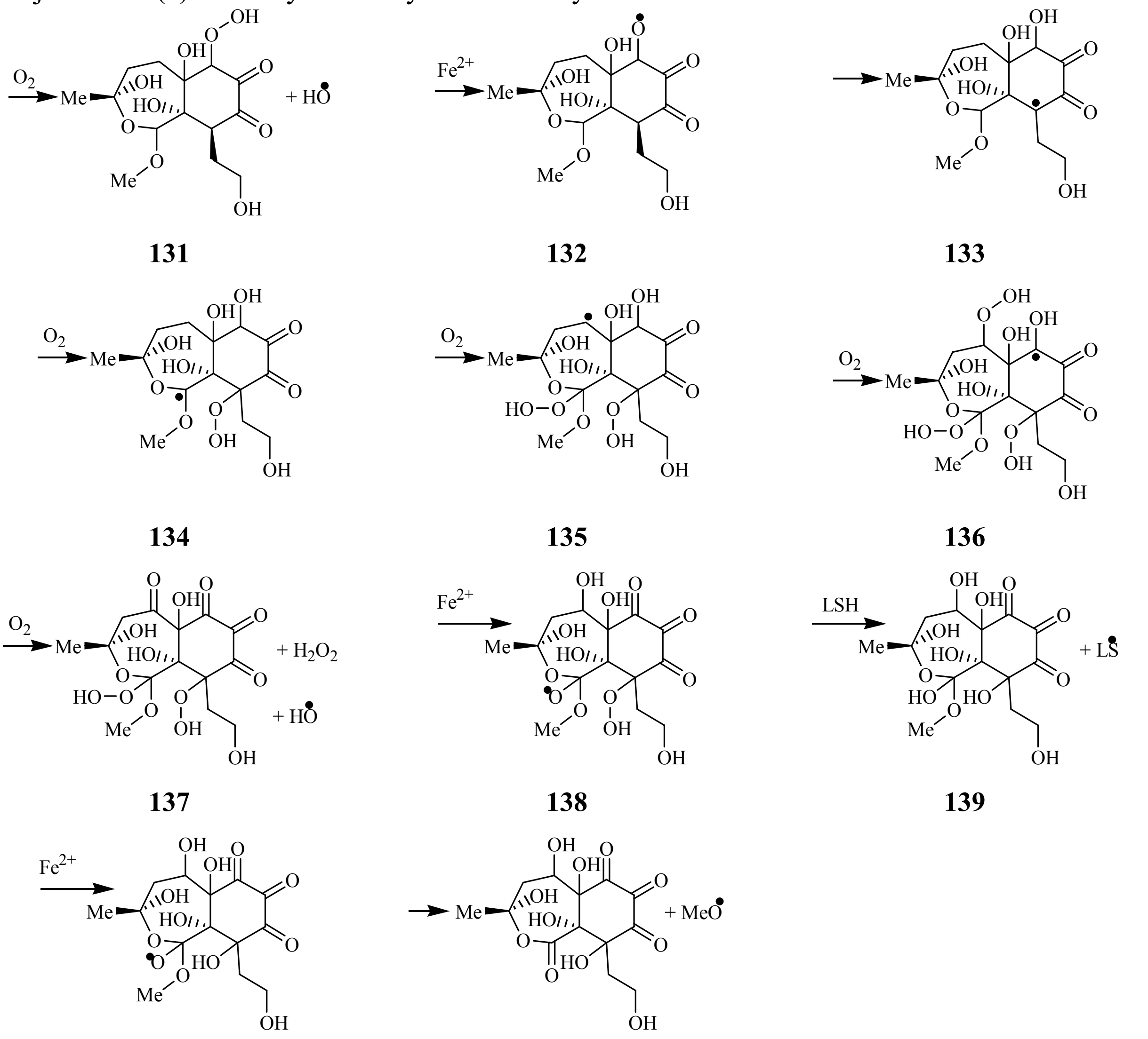

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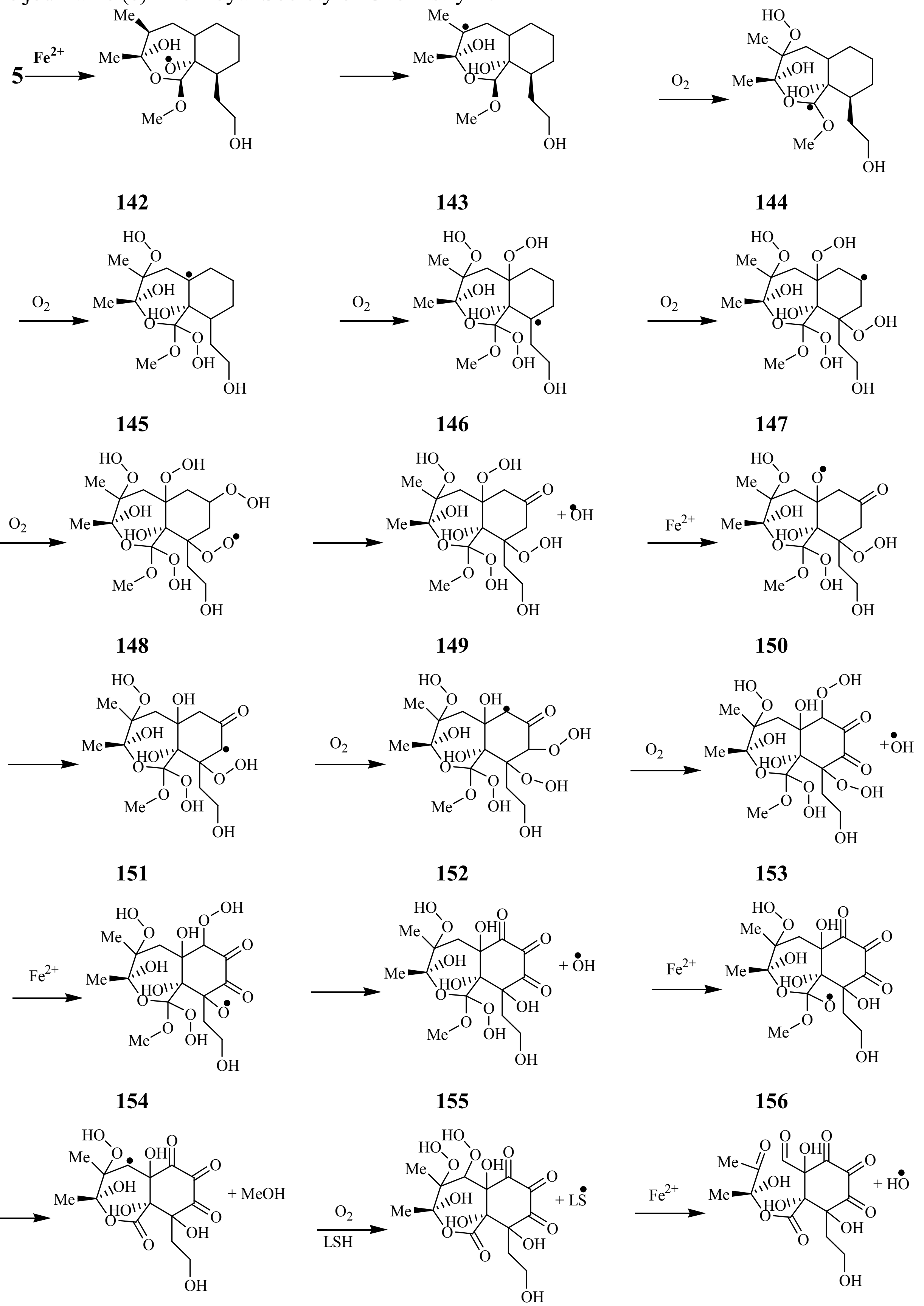
Scheme 4 Stages of the intramolecular oxidation of radical RO[1]$^{\bullet}$**(4).** Kinetic characteristics (Δ*H, E, k*) of elementary steps of the intramolecular oxidation of compound **5** are given in Table 6.

The formed methoxy radical reacts preferentially with LSH forming LS$^{\bullet}$ radical. So, the final yield of free radicals per radical RO[1]$^{\bullet}$**(4)** is as follows: 3 HO$^{\bullet}$ and 2 LS$^{\bullet}$. The total yield of free radicals *via* oxidation of compound **4** is 3 HO$^{\bullet}$ + 1.5 LS$^{\bullet}$.

The introduction of the methyl group in position 4 in such a way that the C^4–H bond is available for RO[1]$^{\bullet}$ intramolecular attack of compound **3** changes the situation dramatically (see Scheme 5).



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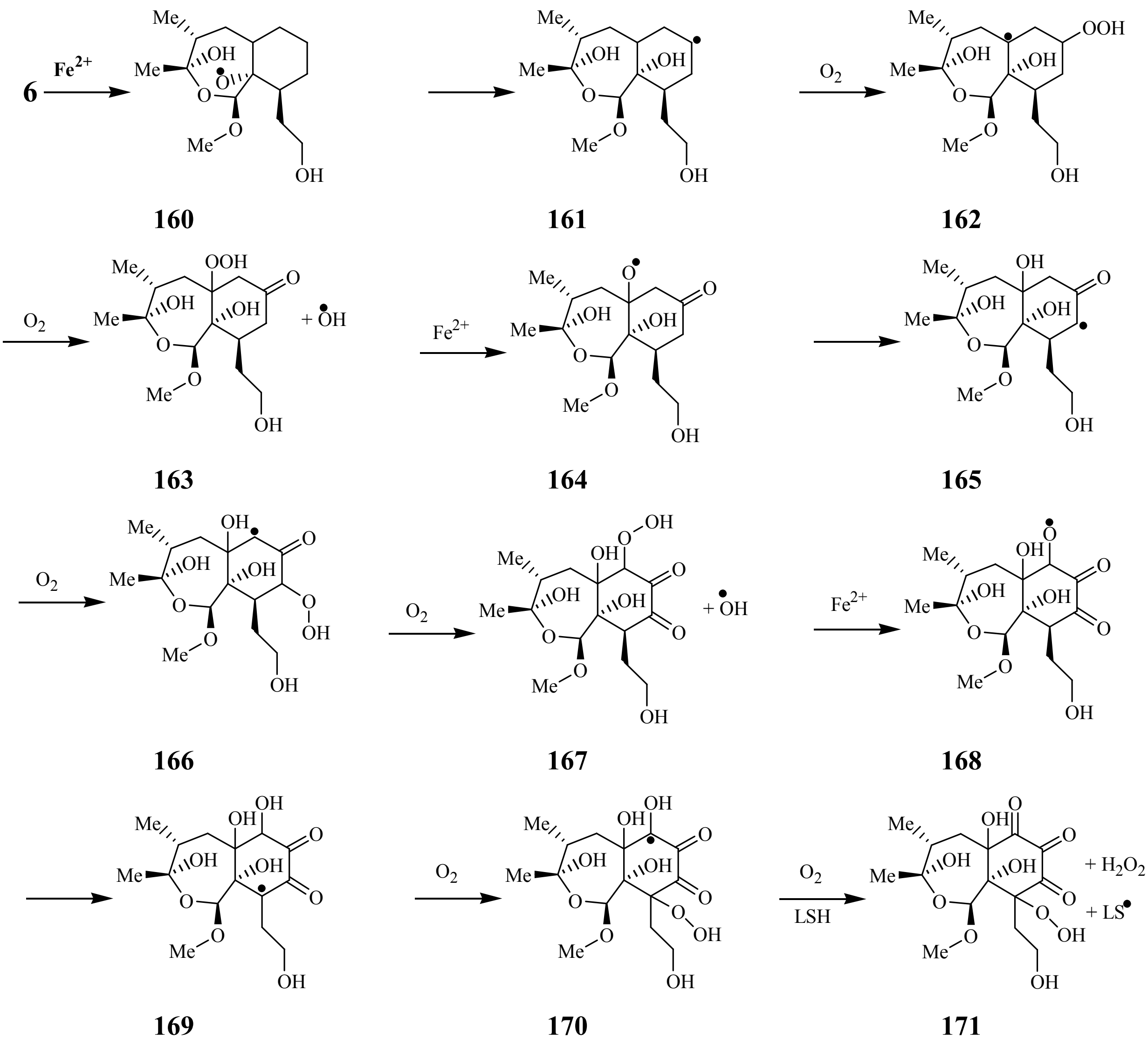
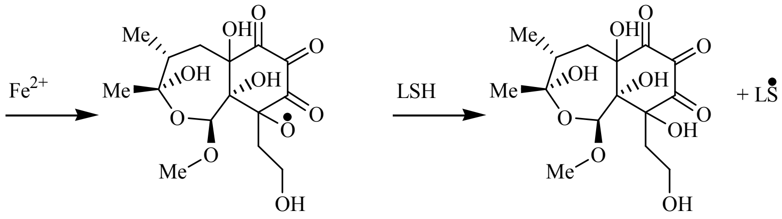
Scheme 5 Stages of the intramolecular oxidation of radical RO[1]• **(5).** Kinetic characteristics (Δ*H*, *E*, *k*) of elementary steps of the intramolecular oxidation of compound **5** are given in Table 6.

The methyl group decreases the bond dissociation energy of the adjacent C^4–H bond, and practically all $RO^{1\bullet}$(**5**) radicals are transformed into radical $R^{4\bullet}$(**5**). The latter is oxidized with the generation of four hydroxyls and one thiyl radical. The total yield of $HO^\bullet$ radicals is as much as 3.75 $HO^\bullet$ + 1.5 $LS^\bullet$, which is higher than that for **1**! This is in agreement with the antimalarial activity of **5**, which is twice as large as that of **1.**[24]

The change in methyl group orientation at the C^4 atom affects very strongly the antimalarial activity of compound **6**.[24] In this compound, the C^4–H bond cannot be attacked by $RO^{1\bullet}$ radical, and the oxidation proceeds in another way (see Scheme 6). As a result, the oxidation of $RO^{1\bullet}$ radical generates only two hydroxy and two $LS^\bullet$ radicals. The total yield of $HO^\bullet$ radicals is equal to 2.5 $HO^\bullet$ and that of thiyl radicals is 1.5.





172 **173**

Scheme 6 Stages of the intramolecular oxidation of radical RO$^{1\bullet}$**(6).** Kinetic characteristics (Δ*H, E, k*) of elementary steps of the intramolecular oxidation of compound **6** are given in Table 6.

Table 6. Kinetic characteristics (Δ*H, E, k*) of elementary steps of the intramolecular oxidation of compounds **3-6**

Reaction	Δ*H* (kJ mol^{-1})	*E* (kJ mol^{-1})	*k* (310 K) (s^{-1})
48 → 49, 92 → 93, 142 → 143	–48.5	17.0	5.46×10^{9}
49 → 50, 50 → 51, 73 → 74	19.7	44.5	1.74×10^{5}
51 → 52	29.2	49.5	2.51×10^{4}
52 → 53, 145 → 146	36.9	54.6	3.47×10^{3}
53 → 54, 86 → 87	45.3	57.4	1.22×10^{3}
54 → 55, 74 → 75, 76 → 77, 87 → 88, 147 → 148	–6.9	19.8	4.15×10^{6}
55 → 56, 64 → 65, 65 → 66, 88 → 89, 108 →109	12.5	42.7	3.51×10^{5}
59 → 60, 165 → 166	43.3	56.3	1.80×10^{3}
60 → 61, 120 → 121	13.5	41.5	2.03×10^{2}
63 → 64, 107 → 108, 156 → 157,	–34.6	21.8	8.51×10^{8}
67 → 68, 85 → 86, 114 → 115, 128 → 129, 132 → 133	–43.0	18.4	3.17×10^{9}
68 → 69, 95 → 96, 146 → 147	50.2	60.0	4.27×10^{2}
69 → 70	30.0	49.4	2.61×10^{4}
70 → 71, 77 → 78, 83 → 84, 113 → 114, 126 → 127, 148 → 149, 162 → 163	17.2	43.2	2.88×10^{5}
72 → 73, 168 → 169	–53.2	14.9	1.23×10^{10}
75 → 76	49.5	57.7	1.04×10^{3}
80 → 81, 80 → 81, 90 → 91, 138 → 139,	–78.5	5.8	2.06×10^{6}

170 → 171, 172 → 173			
4 → 125, 3 → 82, 101 → 102, 111 → 112, 124 → 125, 128 → 129, 160 → 161	–29.7	23.6	4.26×10^{8}
82 → 83	22.1	45.7	1.10×10^{5}
93 → 94, 133 → 134, 143 → 144	19.5	44.3	1.79×10^{5}
94 → 95, 165 → 166	32.6	50.7	1.54×10^{4}
96 → 97	38.4	53.7	4.95×10^{3}
97 → 98	10.3	40.0	1.00×10^{6}
99 → 100	–67.6	10.3	7.35×10^{10}
102 → 103	34.0	53.0	4.00×10^{2}
103 → 104	–2.1	31.0	1.20×10^{2}
109 → 110	8.0	40.6	7.93×10^{5}
112 → 113	–9.3	31.5	2.48×10^{7}
115 → 116	26.7	47.8	4.85×10^{4}
116 → 117	39.0	54.0	4.37×10^{3}
117 → 118, 157 → 158	–5.5	29.5	5.35×10^{2}
119 → 120, 135 → 136	22.9	46.0	7.93×10^{5}
123 → 124	–71.9	1.5	1.12×10^{7}
129 → 130, 151 → 152	28.6	48.7	3.36×10^{4}
130 → 131	2.5	36.5	3.89×10^{6}
134 → 135	41.0	56.6	1.59×10^{3}
136 → 137	8.8	41.0	6.79×10^{5}
144 → 145	27.1	48.0	1.49×10^{8}
150 → 151, 164 → 165	–44.4	18.2	3.41×10^{9}
152 → 153	–8.2	32.0	2.23×10^{7}
154 → 155	–77.4	3.3	2.78×10^{12}
161 → 162, 125 → 126	24.5	46.7	7.32×10^{4}
166 → 167	–4.4	33.6	2.82×10^{7}
169 → 170	15.2	43.8	2.25×10^{5}