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Oxidation of Natural Compounds Catalyzed by Mn(III) Porphyrin Complexes

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Abstract: The oxidation of 1,8-cineole (**1**) and methyl dehydroabietate (**8b**) by hydrogen peroxide, catalysed by Mn(III) porphyrin complexes, is reported. Five oxygenated products (**2-6**) have been obtained from reactions at positions 2 and 3 of 1,8-cineole and three oxygenated products (**9-11**) from the reaction at position 7 of methyl dehydroabietate.

1,8-Cineole (**1**), is one of the major components of the essential oils of several plant species, and specifically *Eucalyptus globulus* Labill., in which it represents up to 70 % of the total oil content of the leaves.[1] Despite its abundance and mainly due to the fact that it is a rather inert compound,[2] 1,8-cineole has little or no use as a raw material for conversion into more valuable products. However some publications have appeared in the last fifteen years dealing with transformations of (**1**) into mixtures of oxygenated products in various positions, by chemical[3,4] or biological[5,6] processes.

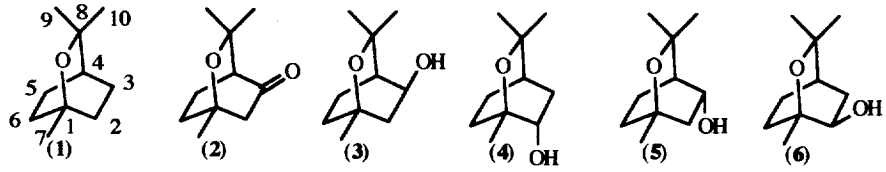
Dehydroabietic acid (**8a**) can be obtained by dehydrogenation of abietane type resin acids. Portugal is a very important pine gum producer,[7] mainly from *Pinus pinaster* Ait. and *Pinus pinea* L. Gum rosin is mainly composed of diterpenic acids, commonly known as resin acids, from which abietic acid (**7**) is one of the most important compounds. Rosin finds many industrial applications,[8] and it is also a valuable source for the syntheses of several compounds with antifungal activity. It has been demonstrated that oxygenated derivatives of dehydroabietic acid (**8a**), like ketone (**9**) and alcohols (**10**) and (**11**), show strong antifungal activity.[9] These compounds were usually obtained by the oxidation of (**8a**) with chromium trioxide[10] or with potassium permanganate.[11]

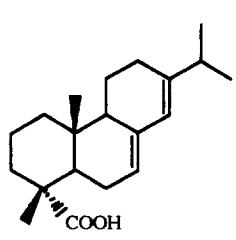
During the last decade, the development of synthetic systems mimicking cytochrome P_{450} activity, using metalloporphyrin catalysts and various oxygen atom donors, have been reported.[12] As a part of an investigation to convert natural products into novel and more valuable compounds the oxidation of (**1**) and (**8b**) with H_2O_2, catalyzed by several manganese porphyrins (**12-15**), was investigated in this work. Imidazole and ammonium acetate were also tested as cocatalysts.[12, 13]

The products (**2-6**) obtained from the oxidation of 1,8-cineole result mainly from oxygenation at positions 2 and 3, and were identified by comparing GC-MS and NMR results with available analytical data.[3,4] By GC-MS two m/z values were found for the products obtained, m/z=168 for ketone (**2**) and m/z=170 for alcohols (**3-6**). The alcohols (**3-6**) were identified based on the characteristic signals on their ^{1}H-NMR specra for the proton vicinal to the hydroxil group: for compound (**3**), δ=4.15 ppm; for compound (**4**), δ=3.73 ppm; for compound

(**5**), δ=4.47 ppm and for compound (**6**), δ=3.50 ppm. The ketone (**2**) was identified by the protons at position 2 that showed two characteristic doublets at δ=2.23 ppm (H_6 endo) and δ=2.35 ppm (H_6 exo).

The ketone (**9**) and the alcohols (**10**) and (**11**) were obtained from the oxidation of methyl dehydroabietate (**8b**) and result from oxygenation at position 7 of (**8b**). These products were analysed by MS, by comparison with a MS library, and by ^{1}H-NMR, comparing with available analytical data.[14,15] The identification of ketone (**9**) was confirmed based on the disappearence of the multiplet at δ=2.92 ppm corresponding to H_7 in (**8b**) and also on the shifts induced in the protons H_{11}=7.30 ppm (d), H_{12}= 7.41 ppm (dd), H_{14}=7.88 ppm (d) and H_6= 2.72 ppm (dd) [for (**8b**): H_{11}=7.17 ppm (d), H_{12}= 7.00 ppm (dd), H_{14}=6.88 ppm (d) and H_6= 1.69-1.93 ppm (m)]. The ^{1}H-NMR of the fractions identified by MS as the alcohols (**10**) and (**11**) showed two signals with chemical shifts characteristic of benzylic protons with a vicinal hydroxil group, and were therefore attributed to H_7. One of these signals was a doublet at δ=4.73 ppm (J=3.33 Hz) which was attributed to $H_{7\beta}$ of alcohol (**11**). The other signal was a triplet at δ=4.86 ppm (J=8.64 Hz), which was attributed to $H_{7\alpha}$ of alcohol (**10**). Both alcohols showed characteristic shifts for protons H_{11}=7.20 ppm (d), H_{12}= 7.13 ppm (dd) and H_{14}=7.22 ppm (d) and H_6= 2.90 ppm (m).





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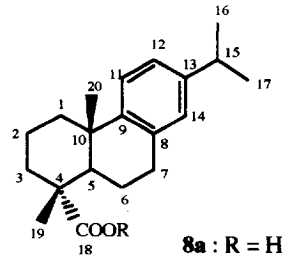

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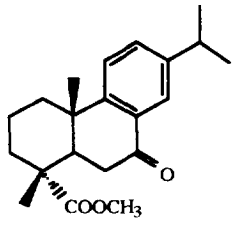
8a : R = H
8b : R = CH_3

Taking into account the yields and numbers of products obtained using catalyst (**12**), (Table 1), it could be concluded that ammonium acetate is a more efficient cocatalyst than imidazole, allowing higher conversion of substrate (**1**) with shorter reaction times, smaller amounts of H_2O_2 and without loss of selectivity. It was also observed that porphyrins (**12**) and (**13**) are more selective catalysts than (**14**) and (**15**) (Table 1), providing 3-keto-1,8-cineole (**2**) and 3-*endo*-hydroxy-1,8-cineole (**5**) as the major products. The results obtained using porphyrins (**14**) and (**15**) show that a higher conversion of (**1**) was achieved when a β-nitro group is present on the porphyrin macrocycle, although with loss of selectivity since products (**3**) and (**6**) were also formed although in low yields. The alcohol (**3**) could only be obtained using catalyst (**15**). It can be seen from Table 2 that alcohol (**11**) was always more abundant than its stereoisomer (**10**), which can be explained based on the steric hindrance caused by the two methyl groups in positions 19 and 20, which makes difficult the approach of the porphyrin on that side of the molecule.

Work in our laboratory is underway to test these and similar catalysts with different substrates.



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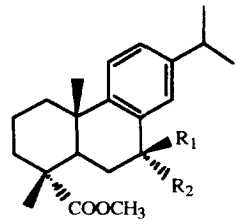
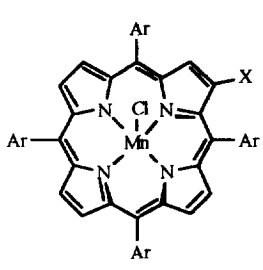
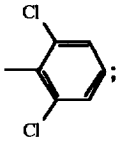
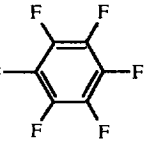


10 : R_1=OH, R_2=H
11 : R_1=H, R_2=OH



(12) X= H, —Ar =  ; **(13)** X= H , —Ar = 

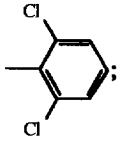
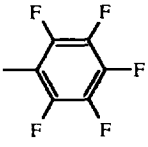
(14) X= NO_2, —Ar =  ; **(15)** X= NO_2 ,—Ar = 

Table 1. Oxidation of 1,8-Cineole (**1**) with H_2O_2 Catalyzed by Mn(III) Porphyrin Complexes (**12-15**)

Catalyst	Time	Product yields (%)[a]					Conversion
	(h)	(**2**)	(**3**)	(**4**)	(**5**)	(**6**)	of (**1**) (%)
No catalyst	12.0	0.0	0.0	0.0	0.0	0.0	0.0
Mn(TDCPP)Cl (**12**)	5.0[b]	11.2	0.0	3.1	12.2	0.0	26.5
Mn(TDCPP)Cl (**12**)	3.7[c]	14.6	0.0	3.6	14.4	0.0	32.6
Mn(TF_5PP)Cl (**13**)	6.0[c]	5.8	0.0	2.8	4.9	0.0	13.5
Mn(TDCPNO_2P)Cl (**14**)	6.3[c]	12.8	0.0	2.9	13.6	3.6	32.9
Mn(TF_5PNO_2P)Cl (**15**)	3.5[c]	9.6	3.3	6.7	11.6	2.4	33.6

[a]Calculated from the peak areas obtained by GC. Reaction conditions: [b]initial progressive addition of 5.0 ml of H_2O_2 (30 %) over 2 h to a solution of substrate : imidazole : MnP (85 : 13.8 : 1) in CH_2Cl_2 : CH_3CN (1 : 1); [c]initial progressive addition of 0.4 ml of H_2O_2 (3 % in CH_3CN) over 2h to a solution of substrate : NH_4OAc : MnP (80 : 6 : 1) in CH_2Cl_2 : CH_3CN (1 : 1).

Table 2. Oxidation of methyl dehydroabietate catalysed by Mn(III)-porphyrin complexes

catalyst	Time	Product yields (%)[a]		Ratio[b]	Conversion
	(h)	(**9**)	(**10**+**11**)	(**11**/**10**)	of (**8b**) (%)
No catalyst	24	0.0	0.0	-	0.0
Mn(TDCPP)Cl (**12**)	12	11.2	31.8	2.0	43.0
$Mn(TF_5PP)Cl$ (**13**)	14	6.4	25.4	2.7	31.8
$Mn(TF_5PNO_2P)Cl$ (**15**)	13	7.3	28.5	3.3	35.8

[a]Calculated from the peak areas obtained by GC.[b]Calculated based on integration of H_7 signals in the ^{1}H-NMR spectra of the mixture of the two alcohols. Reaction conditions: [c]initial progressive addition of 0.4 ml of H_2O_2 (10 % in CH_3CN) over 2h to a solution of substrate : NH_4OAc : MnP (32 : 6 : 1) in CH_3CN.

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