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Article

Synthetic Studies with *Pinus elliottiis´ Rosin* Derivatives. Oxidation of Maleopimaric Anhydride Methyl Ester and Trimethyl Fumaropimarate

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A ozonólise do éster metílico do anidrido maleopimárico na presença de tetracianoetileno produziu um epóxido e um ozonídeo, e a ozonólise do fumaropimarato de trimetila, seguida por tratamento com Me_2S, forneceu um epóxido, um dieno, um ceto-ácido e um produto de oxidação alílica. Alguns dos compostos obtidos apresentaram atividade antibacteriana contra S*taphylococcus aureus, Bacilllus subtilis e Micrococcus luteus.*

Ozonolysis of maleopimaric anhydride methyl ester in the presence of tetracyanoethylene led to an epoxide and an ozonide. Ozonolysis of the trimethyl fumaropimarate, followed by treatment with Me_2S, led to an epoxide, a diene, a keto-acid and an allylic oxidation product. Some of the compounds obtained were active against *Staphylococcus aureus, Bacillus subtilis and Micrococcus luteus.*

Keywords: *Pinus elliottiis' rosin,* oxidation, maleopimaric anhydride methyl ester, trimethyl fumaropimarate.

Introduction

In the search for biologically active substances, we have envisioned that maleopimaric anhydride methyl ester (**1**) and fumaropimaric monomethyl ester (**2**), easily prepared through Diels-Alder reaction of abietane acids present in *Pinus elliottiis' rosin*[1] with maleic anhydride and fumaric acid, respectively, would be potential starting materials mainly for the synthesis of some C-17 oxygenated naturally occurring polycyclic systems such as **4**, **5** and **6**[2,3] (Figure 1), if a way could be found to cleave the Δ^{13} double bond in C-ring. Oxidation of **1** and **2** with $KMnO_4$[4,5], RuO_4 and O_3[6-8] has been already studied during the establishment of the correct stereochemistry of the Diels-Alder products. As part of our research program on the use of *Pinus elliottiis' rosin* as chiral synthons[9], we prepared **1** and **2** in order to cleave the Δ^{13} double bond using different conditions. In the present paper, we describe the results of our work on the oxidative transformations of **1** and trimethyl fumaropimarate (**3**), from which two new compounds were isolated and characterized by spectroscopic data. Some products obtained during our investigation were submitted to biological assays and shown to be active against *Staphylococcus aureus*, *Bacillus subtilis* and *Micrococcus luteus*.

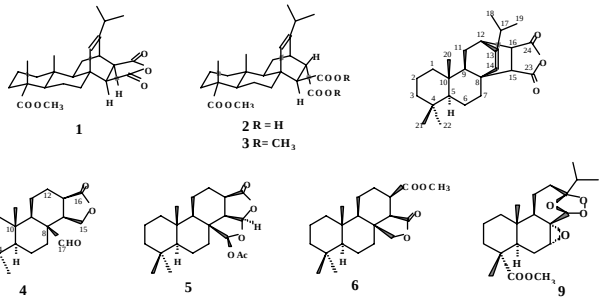

Figure 1

Results and Discussion

It is well known that the product of the ozonolysis of olefins depends on the solvent medium, i.e., protic or aprotic[10]. Zalkow[6,7] and Halbrook[8] reported that ozonolysis of **1** and **2** carried out in acetic acid leads to a mixture of many products.

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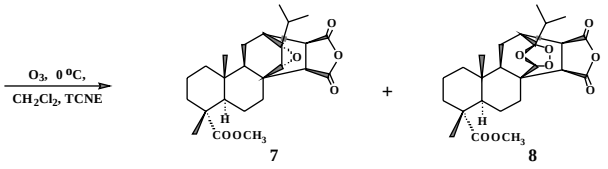
Thus we decided to follow the literature suggestion[11] to carry out the ozonolysis of **1** at 0°C in CH_2Cl_2 solution in the presence of tetracyanoethylene (TCNE) in attempt to minimize the formation of the undesired products obtained previously by Zalkow[4,6,7] and Halbrook[8]. Although in this case the mechanism is not clear, the catalytic action of TCNE on the alcoholysis of epoxides is well known due to its π-acid and one-electron acceptor properties[12]. Carrying out the reaction under these conditions we isolated, after purification, a known epoxide **7**[7] in 20% yield and the ozonide **8** in 7% yield (Scheme 1). This ozonide proved to be stable at low temperature[13] and has not been observed before; this is not surprising since there are reports in the literature concerning the isolation of many stable ozonides[14,15]. The ozonide was characterized by careful analysis of ^1H and ^{13}C NMR data. The hydrogen H-14 appeared at δ 3.19 as a singlet and the carbons C-13 and C-14 of ozonide appeared, respectively, at δ 112.5 and 106.6. These chemical shifts are in good agreement with those observed for the ozonide of methyl abietate (**9**) previously prepared in our laboratory[9].

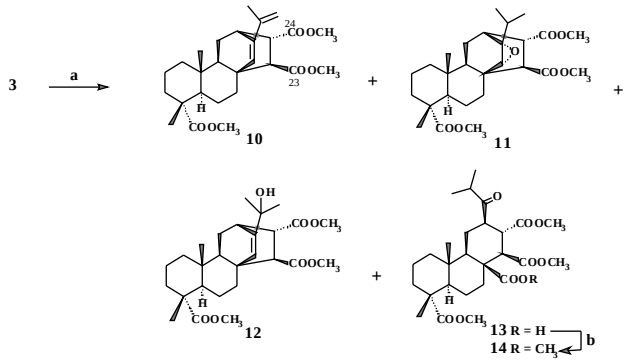


Scheme 1

On the other hand, epoxide **7** was the only product isolated from the ozonolysis of **1**, in the absence of tetracyanoethylene (-78°C; CH_2Cl_2, 20% yield), after treatment with Me_2S. An intractable mixture was obtained when the reaction mixture was treated with $NaBH_4$ or Zn/HOAc. The reaction of **1** with RuO_4 (25°C; CH_2Cl_2; $NaIO_4$/$RuCl_3$)[16,17] also gave the epoxide **7** in 10% yield and did not cleave the Δ[13] double bond to the corresponding keto-acid.

In contrast, ozonolysis of **3** (0°C; CH_2Cl_2), followed by treatment with Me_2S furnished, as expected, the known diene **10** (10% yield)[6], epoxide **11**[7] (19% yield), alcohol **12**[6] (18% yield) and the desired keto-acid **13** which was characterized as tetramethyl ester **14** after methylation with diazomethane (32% yield) (Scheme 2). The ^{13}C NMR spectrum of **14** showed two new carbonyl carbons [at δ 214.6 (C-13, ketone) and at δ 171.8 (C-14, ester)][18]. The ^1H NMR spectrum showed four carbomethoxyl groups (at d 3.57; 3.62; 3.64 and 3.66) which was confirmed by ^{13}C NMR data (at δ 51.7, 51.8 and 51.9 (2x)).

Although Zalkow[4,5] reported the oxidation of **3** with $KMnO_4$ in basic medium leading to a mixture of products, our protocol was carried out using recent and improved conditions described in the literature: *a*)[19] $KMnO_4$ with dibenzo-



Scheme 2. a) O_3, CH_2Cl_2, 0°C; b) CH_2N_2

18-crown-6; CH_2Cl_2; 25°C; 24 h; *b*)[20] $KMnO_4$ supported on silica gel; CH_2Cl_2; 25°C; *c*)[21,22] $KMnO_4$ (cat.) with $NaIO_4$; K_2CO_3; H_2O/t-BuOH; 70°C; 160 h, in hope to obtain a better yield of **13**. Nevertheless, in all cases, the reaction was incomplete and led to an intractable mixture of products.

The desired keto-acid **13** was obtained in only moderate yield and the present result showed that ozonation seems to be the best way to oxidize the hindered Δ[13] double bond of **3**. The easiest ozonolysis of **3**, in comparison with **1**, is probably due to the less hindered α-orientation of the carbomethoxyl group at C-24.

The compounds obtained from the oxidation of **1** and **3** were evaluated for antibacterial activity by means of bioautographic tests, following the methodology previously described[23-24] using chloramphenicol as standard. Compounds **1**, **2**, **12** and **14** proved to be active against gram-positive bacteria (*Bacillus subtilis, Micrococcus luteus, Staphylococcus aureus*) and were submitted to tests for the determination of the Minimal Inhibitory Concentration (MIC) following the cylinder-cup method[25]. MIC values are presented in Table 1 and as can be seen, compound **12** was the most active against the gram-positive bacteria. In contrast, *Salmonella chokerauesuis*, a gram-negative bacteria, was resistant to every substance tested.

Further investigation of the synthesis of some C-17 oxygenated polycyclic systems are underway in our laboratory.

Experimental

All melting points were determined on Kofler block and are uncorrected. TLC was performed on silica gel with fluorescent indicator on glass plates (Silica gel GF_{254}, Merck). Column chromatography was carried out on silica gel (Silica gel 60, 0.06-0.2 mm, Merck). NMR spectra were measured on Varian Gemini - 300 and Bruker ACP - 300 (^1H NMR at 300 MHz, ^{13}C at 75.6 MHz) instruments, in deuterated chloroform with tetramethylsilane as internal standard. IR spectra were measured on FT IR Perkin-Elmer 16 PC. Optical

measurements were run in chloroform, on a polarimeter Carl Zeiss Jena Polamat A. Mass spectra were measured on a high resolution Micromass Autospec (Manchester, UK) spectrometer, using the EI (electron energy 70 eV), source temperature 200°C and resolution 10,000.

Maleopimaric anhydride methyl ester (**1**). *Pinus elliottiis' rosin* was esterified with dimethylsulfate (NaOH, Na_2CO_3/H_2O, Me_2SO_4). After purification by column chromatography with hexane-ethyl acetate mixture (95:5), the mixture of methyl esters was reacted with maleic anhydride according to the literature[4] to give compound **1** (38 % yield) as a colorless crystals: $[\alpha]^{20}_D$ -31.4 (*c* 3.0, $CHCl_3$); mp 211-213°C; IR (KBr, cm^{-1}): 2927, 1781, 1720. 1462, 1242, 1222, 1082, 918; ^1H NMR ($CDCl_3$, δ ppm): 5.53 (s, 1H), 3.67 (s, 3H), 3.09 (m, 1H), 3.08 (dd, *J* = 3; 11 Hz, 1H), 2.71 (d, *J* = 11 Hz, 1H), 2.51(dt, *J* = 3; 14Hz, 1H), 2.23 (m, 1H), 1.80-1.35 (m, 11H), 1.30-1.15(m, 2H), 1.15 (s, 3H), 1.00 (d, *J* = 6,8 Hz, 3H), 0.99 (d, *J* = 6,8 Hz, 3H), 0.59 (s, 3H); ^{13}C NMR: see Table 2; HRMS Calcd. for $C_{25}H_{34}O_5$ 414.2406, Found 414.2407 (M^+).

Trimethyl fumaropimarate (**3**). Compound **2** was prepared according to the literature procedure[26] in 46 % yield. Treatment of **2** with ethereal diazomethane at 0°C led to product **3** (99 % yield) as a viscous liquid: $[\alpha]^{20}_D$ +27.4 (*c* 2.5, $CHCl_3$); IR (KBr, cm^{-1}): 2951, 1730, 1710, 1435, 1385, 1267, 1199, 1177; ^1H NMR ($CDCl_3$, δ ppm): 5.33 (s, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 3.57 (s, 3H), 2.86 (m, 1H), 2.78 (d, *J* = 6 Hz, H-22), 2.57 (dd, *J* = 3; 6 Hz, 1H), 2.38 (m, 1H), 1.10 (s, 3H), 1.80-1.20 (m, 12H), 1.04 (d, *J* = 7 Hz, 3H), 1.03 (d, *J* = 7 Hz, 3H), 1.10-0.80 (m, 2H), 0.56 (s, 13H); ^{13}C NMR: see Table 2; HRMS Calcd. for $C_{27}H_{40}O_6$ 460.2824, Found 460.2822 (M^+).

Ozonolysis of maleopimaric anhydride methyl ester (**1**). A rapid stream of ozone containing approximately 3% of O_3 in O_2 was passed through a solution of **1** (250 mg;

Table 1. Minimal Inhibitory Concentration (MIC) in mg/mL for compounds **1**, **2**, **12** and **14**.

Compound	*Bacillus subtilis* CCT 0089	*Micrococcus luteus* CCT 2720	*Staphylococcus aureus* CCT 4295
1	100	>250	200
2	100	>250	100
12	50	100	50
14	75	100	100

Table 2 - ^{13}C-NMR Chemical Shifts of **1**, **3**, **7, 8, 10-12**, **14** (δ in ppm from TMS, $CDCl_3$)

Carbon	1	3	7	8	10	11	12	14[d]
1	38.0	37.8	37.8	37.6	37.5	37.7	37.8	38.1
2	16.9	17.1	16.9	17.2	17.1	17.3	17.1	17.7
3	36.5	36.9	36.5	36.5	36.9	36.6	36.8	36.6
4	47.0	47.3	46.8	46.9	47.0	47.0	47.3	47.4
5	49.4	49.6	49.1	50.0	49.6	49.1	49.5	50.7
6	21.6	21.9	21.7	20.4	21.9	21.4[b]	21.9	22.3[b]
7	34.7	34.8	33.3	36.5	34.4	33.6	34.7	36.5
8	40.4	41.4	40.7	47.4	41.4	39.5	41.6	46.6
9	53.3	54.7	52.7	52.6	55.1	52.8	54.3	57.5
10	37.8	37.8	36.5	37.5	37.4	37.3	37.7	37.3
11	27.2	23.7	24.2	24.1	23.1	21.9[b]	23.9	22.6[b]
12	35.7	35.9	33.3	40.1	33.3	34.3	34.1	50.2
13	148.1	148.8	65.7	112.5	139.5	63.5	149.0	214.6
14	125.1	124.7	59.5	106.6	130.0	57.5	125.2	171.8
15	53.1	54.2	52.7	53.3	54.1	51.6	54.1	57.2
16	45.7	48.8	43.7	42.2	49.0	44.9	49.0	42.8
17	32.7	32.8	26.9	34.1	142.5	27.4	72.2	38.9
18	19.9[a]	20.5	15.0[a]	16.1[a]	20.0	15.0[a]	27.8[a]	18.0[a]
19	20.5[a]	20.5	16.9[a]	16.4[a]	110.0	17.6[a]	28.0[a]	18.8[a]
20	15.5	16.0	14.7[a]	15.6[a]	15.7	15.5[a]	16.1	14.3
21	16.7	16.7	16.9	16.5	16.7	16.6	16.7	16.2
22	179.0	179.9	179.1	179.1	179.6	179.0	179.9	178.8
23	171.0	174.8	171.8	171.5	174.6	172.8	174.6	173.2
24	172.7	175.4	173.4	173.2	175.7	175.2	175.7	174.1
OMe	52.0	52.1[c]	51.9	52.0	52.1[c]	51.9[c]	51.7[c]	51.9[c]
OMe		51.5[c]			51.7[c]	51.4[c]	52.1[c]	51.7[c]
OMe		52.1[c]			52.3[c]	52.2[c]	52.3[c]	51.9[c]
OMe								51.8[c]

[a, b, c] May be interchanged; [d] the original numbering for carbons was used

0.60mmol) and tetracyanoethylene (102 mg; 0.79 mmol) in 20 cm^3 of dichloromethane at 0°C for 2h until the blue color of excess of ozone was present. The solvent was removed in a rotary evaporator and residue was purified by column chromatography with a hexane-ethyl acetate mixture (7:3 - 1:1) obtaining two products:

Compound **7**: (51 mg; 0.12 mmol; 20%) as an amorphous solid: $[\alpha]^{20}_D$ -11.6 (c 3.3 $CHCl_3$); mp 285-287°C; IR (KBr, cm^{-1}): 2923, 1776, 1718, 1467, 1384, 1261, 1231, 1095, 920; ^1H NMR ($CDCl_3$, δ ppm): 3.67 (s, 3H), 3.19 (s, 1H), 2.82 (dd, *J* = 3; 11 Hz, 1H), 2.80 (m, 1H), 2.64 (dt, *J* = 3; 14 Hz, 1H), 1.80-1.36 (m, 11H), 1.30-1.18 (m, 2H), 1.24 (m, 1H), 2.43 (d, *J* = 11 Hz, 1H), 1.95 (m, 1H), 1.18 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.82 (s, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: see Table 2; HRMS Calcd. for $C_{25}H_{34}O_6$ 430.2355, Found 430.2357 (M^+);

Compound **8**: (20 mg; 0.04 mmol; 7%) as an amorphous solid: $[\alpha]^{20}_D$ -22.4 (*c* 3.0 $CHCl_3$); mp 193-195°C; IR (KBr, cm^{-1}): 2940, 1776, 1719, 1461, 1255, 1233, 1105, 942; ^1H NMR ($CDCl_3$, δ ppm): 5.62 (s, 1H), 3.67 (s, 3H), 3.07 (t, *J* = 5 Hz, 1H), 3.03 (dd, *J* = 4.7; 11 Hz, 1H), 2,75 (d, *J* = 11 Hz, 1H), 2.50 (dt, *J* = 3; 14 Hz, 1H), 2.05 (m, 1H), 1.85-1.40 (m, 11H), 1.57 (m, 1H), 1.35-1.20 (m, 2H), 1.18 (s, 3H), 1.05 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H); ^{13}C NMR: see Table 2; HRMS Calcd. for $C_{25}H_{34}O_8$ 462.2253, Found 462.2254 (M^+).

Ozonolysis of trimethyl fumaropimarate (**3**). A rapid stream of ozone containing approximately 3% of O_3 in O_2 was passed through a solution of **3** (300 mg; 0.65 mmol) in 20 cm^3 of CH_2Cl_2 at 0°C for 2h, until the blue color of excess of ozone was present. Then, oxygen was passed through the solution for removal of excess ozone, dimethyl sulfide (10 drops) was added, and the mixture was stirred 12h at room temperature. After removal the solvent, the residue was purified through column chromatography with hexane-ethyl acetate mixtures (5:5 - 3:7) giving two products:

Compound **10**: (29 mg; 0.06 mmol; 10%) as a viscous liquid: $[\alpha]^{20}_D$ + 50.2 (*c* 2.0 $CHCl_3$); IR (KBr, cm^{-1}): 2949, 1728, 1434, 1387, 1254, 1188, 1172, 737; ^1H NMR ($CDCl_3$, δ ppm): 5.81 (s, 1H), 5.14 (s, 1H), 4.90 (s, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.60 (s, 3H), 3.36 (m, 1H), 2.88 (d, *J* = 6 Hz, 1H), 2.58 (dt, *J* = 2; 6 Hz, 1H), 1.91 (s, 3H), 1.80-1.30 (m, 14H), 1.20-0.80 (m, 2H), 1.13 (s, 3H), 0.52 (s, 3H); ^{13}C NMR: see Table 2; HRMS Calcd. for $C_{27}H_{38}O_6$ 458.2668, Found 458.2667 (M^+);

Compound **11**: (59 mg; 0.12 mmol; 19%) as a viscous liquid: $[\alpha]^{20}_D$ -10.3 (*c* 3.0 $CHCl_3$); IR (KBr, cm^{-1}): 2948, 1727, 1434, 1386, 1254, 1195, 1175, 736; ^1H NMR ($CDCl_3$, δ ppm): 3.74 (s, 3H), 3.66 (s, 3H), 3.62 (s, 3H), 3.13 (s, 1H), 3.04 (m, 1H), 2.88 (dt, *J* = 3; 14Hz, 1H), 2.70 (d, *J* = 6 Hz, 1H), 2.47 (m, 1H), 1.98 (m, 1H), 1.80-1.10 (m, 13H), 1.17 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.80 (s, 3H), 0.76 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: see Table 1; HRMS Calcd. for $C_{27}H_{40}O_7$ 476.2774, Found 476.2774 (M^+);

Compound **12**: (50 mg; 0.11 mmol; 18%) as a viscous liquid: $[\alpha]^{20}_D$ +18.3 (*c* 3.2 $CHCl_3$); IR (KBr, cm^{-1}): 3490, 2950, 1724, 1435, 1387, 1254, 1194, 1175, 737; ^1H NMR ($CDCl_3$, δ ppm): 5.62 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.60 (s, 3H), 3.15 (brs, 1H), 2.86 (d, J = 6 Hz, 1H), 2.59 (dt, J = 3; 6 Hz, 1H), 1.90-0.90 (m, 15H), 1.39 (s, 6H), 1.13 (s, 3H), 0.58 (s, 3H); ^{13}C NMR: see Table 2; HRMS Calcd. for $C_{27}H_{40}O_7$ 476.2774, Found 476.2775 (M^+);

Compound **13**: (110 mg; 0.21 mmol; 32%). This compound was esterified with ethereal diazomethane at 0°C to give product **14** (111 mg; 0.21 mmol; 100%) as an amorphous solid: $[\alpha]^{20}_D$ +37.0 (*c* 2.5 $CHCl_3$); mp 45-46°C; IR (KBr, cm^{-1}): 2959, 1726, 1435, 1240, 1200, 1150; ^1H NMR ($CDCl_3$, δ ppm): 3.73 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 3.57 (s, 3H), 2.94 (dt, J = 4.5; 12Hz, 1H), 2. 80 (m, 1H), 2.41 (d, *J* = 12 Hz, 1H), 2.30 (d, *J* = 12 Hz, 1H), 2.05 (q, *J* = 12 Hz, 1H), 1.95-1.50 (m, 10H), 1.40-1.10 (m, 5H), 1.13 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.73 (s, 3H); ^{13}C NMR: see Table 2; HRMS Calcd. for $C_{28}H_{42}O_9$ 522.2828, Found 522.2826 (M^+).

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