Tetrahedron Vol. 43, No. 22, pp. 5245 to 5250, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

SYNTHESIS OF PYRENOCINES A, B AND PYRENOCHAETIC ACID A

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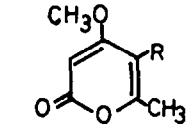
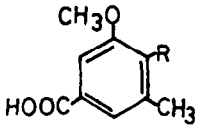
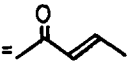
(*Received in Japan* 21 *July* 1987)

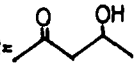
Abstract - Starting from 5-acetyl-4-hydroxy-6-methyl-α-pyrone, three phytotoxins, pyrenocines A, B and pyrenochaetic acid A were synthesized. Retro-Diels-Alder reaction was successfully applied in the synthesis of pyrenochaetic acid A.

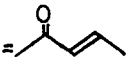
Pyrenocines A (1), B (2)[1] and pyrenochaetic acids A (3), B (4) and C (5)[2] are phytotoxic metabolites isolated from the culture filtrate of Pyrenochaeta terrestris, the causal fungus of onion pink root disease. Pyrenocines A (1) and B (2) inhibited completely lettuce germination at 50 ppm and at 500 ppm, respectively. Among three pyrenochaetic acids, pyrenochaetic aicd A (3) showed the highest phytotoxicity, and inhibited completely the root growth of onion seedlings at 250 ppm and lettuce seedlings at 500 ppm. In this paper, we would like to report the synthesis of three phytotoxins.[3]

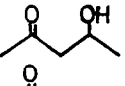


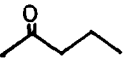


1 R= 

2 R= 

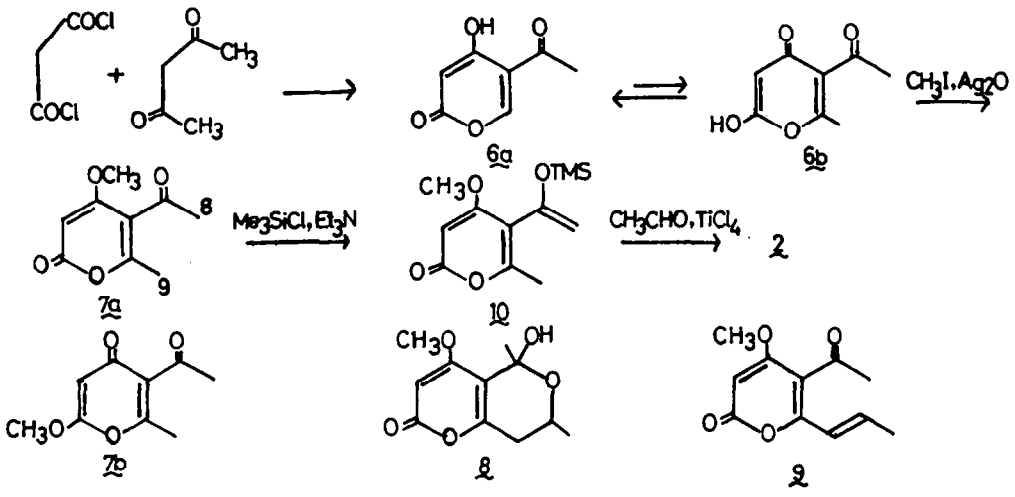
3 R= 

4 R= 

5 R= 

Synthesis of pyrenocines A (1) and B (2). Condensation of acetylacetone and malonyl chloride according to the known procedure[4] afforded a pyrone 6a m.p.159.5 - 161.5°C, to which γ-pyrone structure 6b was erroneously assigned by Butt et al.[4] Validity of the α-pyrone structure 6a was confirmed by the IR spectrum, in which a broad absorption due to intramolecular hydrogen bonding, that is only possible for 6a and not for 6b, was observed at 3200 - 3000 cm^{-1} under high dilute conditions (0.6 x 10^{-3} mole in CCl_4). Further, in the ^{13}C NMR spectrum of 6a, a signal at δ 162.5 due to C-2 of α-pyrone[5] like 7a was observed and no signals characteristic of γ-pyrone[6] carbonyl like 7b appeared near 180 ppm (Table 1). Therefore, α-pyrone structure 6a was assigned to the condensation product. Methylation of 6a with methyl iodide in the presence of silver oxide gave a single product 7a, m.p.103.5 - 104.5°C, in 96.3 % yield. On the other hand, treatment

of 6a with diazomethane afforded the α-pyrone 7a, and a γ-pyrone 7b, m.p.114 - 116°C in a ratio of 7.6 : 1. Structural assignment of these pyrones was deduced from the IR spectra, in which carbonyl



stretching frequency of the α-pyrone ring occurs at 1760 cm^{-1} in 7a, but that of the γ-pyrone ring appears at 1670 cm^{-1} in 7b. Additional better basis for the assignment was obtained by the

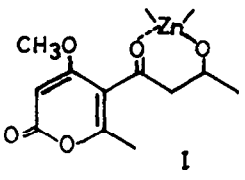
Table 1. ^{13}C NMR spectral data of 6a, 7a and 7b (ppm)

Compd / Carbon no.	Chemical shift (multiplicity)[a,b] 6a	7a	7b
C-2	162.51 (s)	162.30 (s)	167.03 (s)
C-3	90.06 (d)	87.61 (d)	90.13 (d)
C-4	169.43 (s)	168.43 (s)	178.89 (s)
C-5	115.36 (s)	115.70 (s)	125.63 (s)
C-6[c]	168.43 (s)	163.64 (s)	163.41 (s)
C-7	200.25 (s)	197.63 (s)	200.14 (s)
C-8	32.40 (q)	32.13 (s)	31.80 (s)
C-9	20.19 (q)	18.52 (q)	18.11 (q)
C-10	·	56.36 (q)	56.36 (q)

a Abbreviation used are s: singlet, d: doublet, q: quartet.
b Solvents; 6a: acetone-d_6, 7a, 7b: $CDCl_3$
c Two bond carbon-proton coupling constants: 6a ($^2J_{CH}$=7.3 Hz), 7a ($^2J_{CH}$=7.3 Hz), 7b ($^2J_{CH}$=7.7 Hz).

^{13}C NMR spectra (Table 1). Thus, the δ value of around 180 ppm in 7b (178.89 ppm) which would be characteristic of γ-pyrone rings, as can be seen from the literature,[6] is markedly different from the typical value of about 160 ppm found in the spectra of 7a (162.30 ppm) and other α-pyrones.[5] Aldol condensation of 7a with acetaldehyde in the presence of LDA yielded a mixture of 2 and a hemiacetal 8, ^1H NMR $\delta^{CDCl_3}_{TMS}$ 1.27 (3H, d, J=7Hz, CH_3), 1.69 (3H, s, CH_3), 2.40 (2H, d, J=7Hz, CH_2), 3.18 (1H, bs, OH), 3.82 (3H, s, OCH_3), 4.07 - 4.40 (1H, m, CH), 5.43 (1H, s, =C-H), which were able to be separated each other by usual silica gel chromatography. Acetylation of the mixture with acetic anhydride in pyridine yielded a trace amount of pyrenocine A (1) and 9, ^1H NMR $\delta^{CDCl_3}_{TMS}$ 1.89 (3H, dd, J=1.8, 6.0 Hz, =C-CH_3), 2.43 (3H, s, $COCH_3$), 3.86 (3H, s, OCH_3), 5.49 (1H, s, =CH), 6.23 (1H, dq, J=16.5, 1.8 Hz, =CH), 6.92 (1H, dq, J=16.5, 6.0 Hz, =CH). From these results, it is apparent that besides 8-CH_3, 9-CH_3 also reacts with acetaldehyde on the aldol condensation.

In order to control the regioselectivity, the reactions were carried out under various conditions adding zinc chloride, which is able to form a stable, chelated intermediate I[7]. The best result was obtained by the reaction carried out in ether and we obtained 2 and 8 as a mixture (11 %) in ratio of 7.3 : 1. From the mixture, pyrenocine B (2) was isolated in low yield together with rather large amount of the starting material. Therefore, the pyrone 7a was treated with trimethylsilyl chloride to yield silyl enol ether 10. Condensation of 10 with acetaldehyde using titanium tetrachloride in methylene chloride at -76°C[8] afforded pyrenocine B (2), m.p.103.0 - 103.5°C in 40.7 % yield. Synthetic pyrenocine B (2) was identical with natural sample in the ^{1}H NMR and IR spectra. Treatment of 2 with acetic anhydride in pyridine gave quantitatively pyrenocine A (1), m.p.107.3 - 108.3°C.



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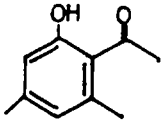
Synthesis of pyrenochaetic acid A (3): Since various attempts to synthesize pyrenochaetic acids starting from closely related benzene derivatives, ie, 2-acetyl-3,5-dimethylphenol (11) and 3-hydroxy-5-methylbenzoic acid (12) have all failed, the α pyrone 7a was chosen as a starting



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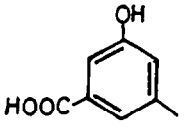

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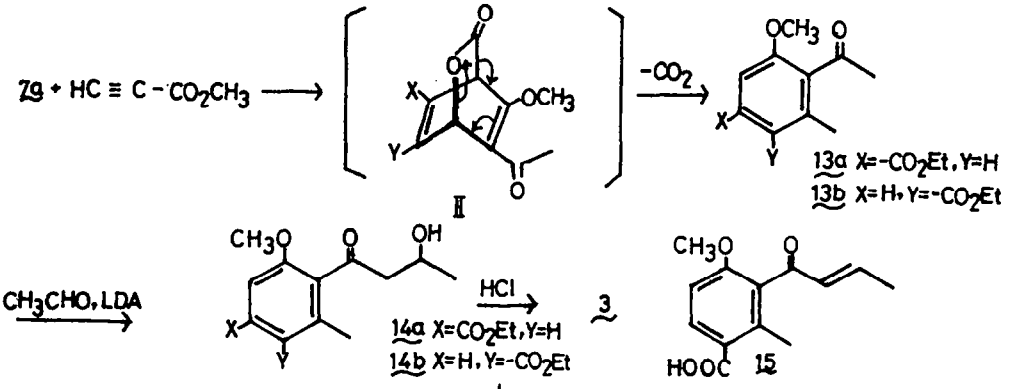
material for present synthesis. It was well known that α-pyrone reacts with propiolate to form benzoates evolving carbon dioxide through retro-Diels-Alder reaction.[9] In fact, the Diels-Alder reaction of the pyrone 7a with ethyl propiolate at 180 - 200°C for 17 hr in a sealed tube afforded, via retro-Diels-Alder reaction[10] evolving carbon dioxide (II), two ethyl benzoates, 13a, m.p.63.1 - 64.1°C and 13b, m.p.43.6 - 46.6°C in a ratio of 2 : 3 in 83.7 % yield. Regiochemistry of the two



benzoates, 13a and 13b, was easily confirmed by the ^{1}H NMR spectra, in which the latter 13b exhibited characteristic ortho coupling constants with the signals at δ 6.78 (1H, d, J=8.8 Hz) and at δ 7.93 (1H, d, J=8.8 Hz). Recently, by the similar procedure, methyl ester of 13a was also prepared from 5-acetyl-6-methoxy-4-methyl-α-pyrone and methyl propiolate.[10] Aldol condensation of the benzoate 13a with acetaldehyde in the presence of LDA in THF yielded a product 14a, m.p.44.2 - 46.2°C in 80.5 % yield. Though alkaline hydrolysis of 14a involved mainly a retro-aldol reaction to give 4-acetyl-3-methoxy-5-methylbenzoic acid, hydrolysis with conc. HCl under refluxing 13 hr afforded pyrenochaetic acid A (3), m.p.172.0 - 176.0°C (lit.[2] m.p.176 - 179°C) in 47.4 % yield. The IR and ^{1}H NMR spectra of synthetic pyrenochaetic aicd A (3) were completely identical with those of natural sample in all respects, and the structure of the phytotoxin was confirmed.

Aldol condensation of the regioisomer 13b in a similar manner gave 14b in 75.9 % yield. Treatment of the product 14b with conc. HCl under refluxing for 17 hr yielded the regioisomer 15

of pyrenochaetic acid (3), in 37 % yield. The isomer 15 showed 80 % inhibition of the root growth of lettuce seedlings at 500 ppm compared with control.

EXPERIMENTAL

All m.ps are uncorrected and were determined on a Yanaco Micromelting Point Apparatus MP-3D. The IR spectra were recorded on a Hitachi IR Spectrometer Model 285 and ^{1}H NMR spectra were obtained with a Hitachi High Resolution NMR Spectrometer Model R-22 (90 MHz), JEOL JNM FX-100 FT-NMR spectrometer (100 MHz), JEOL JNM FX-200 FT-NMR spectrometer (200 MHz) and JEOL JNM FX-400 FT-NMR spectrometer (400 MHz). Mass spectra were determined on JEOL JMS-D300 and JEOL JMS-DISG-2 Mass Spectrometer.

5-Acetyl-4-hydroxy-6-methyl-α-pyrone 6a
A mixture of malonyl chloride (10 ml) and acetylacetone (10 ml) was stirred at room temp. After 5 min, the mixture evolved drastically HCl and darkened. After 15 min the mixture crystallized. The crystals were crushed and washed with ether to give 6a (13 g, 79.4 %), m.p.159.5 - 161.5°C (from THF-ether), (lit[9] m.p.162°C), IR (KBr) cm^{-1}: 1695, 1665, 1620, 1600, 1550, 1495, 1280. IR (0.6 x 10^{-3} mole in CCl_4) cm^{-1}: 3200 - 3000 (broad). ^{1}H NMR $\delta^{CDCl_3}_{TMS}$: 2.26 (3H, s, -CH_3), 2.65 (3H, s, -$COCH_3$), 5.52 (1H, s, =CH), ^{13}C NMR (Table 1).

5-Acetyl-4-methoxy-6-methyl-α-pyrone 7a
a. Methylation with diazomethane: A mixture of 6a (510 mg) and excess amount of ether solution of diazomethane (30 ml) was allowed to stand for 18 hr at room temp. to deposit white crystals. Resultant crystals were collected by filtration. The filtrate was concentrated in vacuo to yield crystals which were recrystallized from ethyl acetate. The same operation with the mother liquor was repeated three to four times to give 7a (252.8 mg). Finally, the filtrate was concentrated to give a residue which was chromatographed on a silica gel column eluting with benzene-ethyl acetate (1 : 1 v/v) to yield 7a (45.7 mg) and 7b (39.5 mg). Combined 7a (338 mg, 61.2 %) was recrystallized from ethyl acetate to give needles; m.p.103.5 - 104.5°C, IR (KBr) cm^{-1}: 1760, 1700, 1620, 1405, ^{1}H NMR $\delta^{CDCl_3}_{TMS}$ 2.28 (3H, s, -CH_3), 2.42 (3H, s, $COCH_3$), 3.87 (3H, s, OCH_3), 5.47 (1H, s, =C-H), ^{13}C NMR (Table 1). MS m/z: 182 (M^+), 167 (M^+-CH_3), 154 (M^+-CO), 137 (M^+-$COOH_3$). HR-MS m/z: 182.0550 (M^+), calc for $C_9H_{10}O_4$ 182.0577. (Found: C, 59.25; H, 5.54 %. $C_9H_{10}O_4$ requires C, 59.34; H, 5.49 %). 7b, m.p.114 - 116°C IR (KBr) cm^{-1}; 1700, 1670, 1630, 1410; ^{1}H NMR $\delta^{CDCl_3}_{TMS}$ ppm: 2.31 (3H, s, CH_3), 2.52 (3H, s, $COCH_3$), 3.87 (3H, s, OCH_3), 5.52 (1H, s, =CH). ^{13}H NMR (Table 1). MS m/z: 182 (M^+), 167 (M^+-CH_3). HR-MS m/z: 182.0558 (M^+), calc for $C_9H_{10}O_4$ 182.0576. (Found: C, 58.09; H, 5.57 %, $C_9H_{10}O_4$ requires C, 59.34; H, 5.49 %).
b. Methylation with CH_3I-Ag_2O: A mixture of 6a (1.44 g), CH_3I (1 ml) and Ag_2O (1.35 g) in chloroform (15 ml) was stirred for 2 hr at room temp. After adding additional Ag_2O (0.5 - 0.7 g) the mixture was stirred for 5 hr. The mixture was filtrated and the residue (Ag_2O) was washed three times with chloroform. Combined filtrates were concentrated in vacuo to give yellow needles (1.45 g, 96.3 %), which were identical with previously obtained 7a in all respects.

4-Methoxy-6-methyl-5-(1-trimethylsilyloxyvinyl)-α-pyrone (10)
A mixture of 7a (500 mg), Me_3SiCl (0.7 ml), Et_3N (0.9 ml) and DABCO (150 mg) was stirred for 48 hr at room temp. To the reaction mixture was added cooled $NaHCO_3$ aqueous solution, and the mixture was extracted with n-pentane. Combined extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo to give very unstable plates 10 (110 mg), ^{1}H NMR $\delta^{CDCl_3}_{TMS}$ ppm 0.20 (9H, s, $OSiMe_3$), 2.32 (3H, s, -CH_3), 3.81 (3H, s, -OCH_3), 4.30 (1H, d, J=1.5 Hz, =CH), 4.66 (1H, d, J=1.5 Hz, =CH), 5.44 (1H, s, =CH).

Pyrenocine B (2)
To a mixture of acetaldehyde (0.018 ml) and $TiCl_4$ (0.035 ml) in dichloromethane (2.36 ml) was added dropwise 10 (75 mg) through syringe for 5 min at -76°C under nitrogen atmosphere, and the mixture was stirred for 3 hr at -76°C. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. Combined extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to give a residue, which was chromatographed on silicic acid column eluting with benzene-ethyl acetate (2 : 1 v/v) to give pyrenocine B (2) as white crystals (15.8 mg, 23.7 %) and 7a (22.4 mg, 41.7 %). The crystals were recrystallized from n-hexane-ether to give pure 2, m.p.103.0 - 103.5°C (lit[1] m.p.97.4 - 99.2°C). Spectroscopic data are identical with those of natural pyrenocine B. HR-MS m/z 226.0845 (M^+), calc for $C_{11}H_{14}O_5$ 226.0804.

Pyrenocine A (1)
A solution of 2 (5 mg) and acetic anhydride (0.1 ml) in pyridine was stirred for 25 hr at room temp. After adding water, the reaction mixture was extracted with ethyl acetate, and combined extracts were washed with $NaHCO_3$ aqueous solution, dried over anhydrous Na_2SO_4, concentrated in vacuo to give crude crystals. The crystals were chromatographed on a silicic acid column using benzene-ethyl acetate (3 : 1 v/v) to yield quantitatively pyrenocine A (2, 4.0 mg). Recrystallization from n-hexane-ether gave pure 2, m.p.107.3 - 108.3°C (lit[1] m.p.110.9 - 111.5°C). Spectral data of the synthetic sample are identical with those of natural pyrenocine A (2). HR-MS m/z 208.0711 (M^+), calc for $C_{11}H_{12}O_4$ 208.0733.

Ethyl 4-acetyl-3-methoxy-5-methylbenzoate 13a and ethyl 3-acetyl-2-methoxy-3-methylbenzoate 13b
A mixture of the pyrone 7a (200 mg, 1.0 mmole) and ethyl propiolate (0.5 ml, 5.80 mmole) was heated at 170 - 200°C for 17 hr in a sealed tube. After cooling, the reaction mixture was concentrated in vacuo to give a residue which was chromatographed on silicic acid column using

benzene-ethyl acetate (98 : 2 v/v) to yield crude 13a (110 mg) as white crystals and 13b (152.1 mg) as yellow crystals. Each of these fractions contained a small amount of trimers of ethyl propiolate. Recrystallization from n-hexane gave pure 13a and 13b. 13a, m.p.63.1 - 64.1°C, IR (KBr) cm^{-1}, 1725, 1695, 1240, 1100; ^1H NMR $\delta^{CDCl_3}_{TMS}$ ppm 1.40 (3H, d, J=7.1 Hz, $-CH_2\underline{CH_3}$), 2.27 (3H, s, $ArCH_3$), 2.49 (3H, s, $COCH_3$), 3.87 (3H, s, $-OCH_3$), 4.38 (2H, q, J=7.1 Hz, $-\underline{CH_2}CH_3$), 7.41 (1H, bs, Ar-H), 7.50 (1H, bs, Ar-H). MS m/z 236 (M^+), 221 (M^+-CH_3), 193 (M^+-COCH_3), HR-MS m/z 236.1046 (M^+), calc for $C_{13}H_{16}O_4$ 236.1046 (Found: C, 66.26; H, 6.93 %. $C_{13}H_{16}O_4$ requires C, 66.10; H, 6.78 %). 13b, m.p.43.6 - 46.6°C, IR (neat) cm^{-1} 1715, 1580, 1265, ^1H NMR $\delta^{CDCl_3}_{TMS}$ ppm 1.38 (3H, t, J=7.1 Hz, $-\underline{CH_2}CH_3$), 2.44 (3H, s, $ArCH_3$), 2.47 (3H, s, $-COCH_3$), 3.85 (3H, s, $-OCH_3$), 4.33 (2H, q, J=7.1 Hz, $-CH_2CH_3$), 6.78 (1H, d, J=8.8 Hz, Ar-H), 7.93 (1H, d, J=8.8 Hz, Ar-H). MS m/z 236 (M^+), 221 (M^+-CH_3), 207 ($M^+-C_2H_5$), 193 (M^+-COCH_3), HR-MS m/z 236.1043 (M^+), calc for $C_{13}H_{16}O_4$ 236.1046 (Found: C, 65.46; H, 6.52 %. $C_{13}H_{16}O_4$ requires C, 66.10; H, 6.78 %).

Ethyl 4-(3-hydroxybutyryl)-3-methoxy-5-methylbenzoate (14a)

A solution of diisopropylamine (0.5 ml) and n-butyl lithium (1.7 ml of 15 % hexane solution) in dried THF (3.0 ml) was stirred for 30 min at -75°C under nitrogen atmosphere. To the mixture was added a solution of 13a (505.5 mg) in THF (2.0 ml) through syringe. After 30 min, a solution of acetaldehyde (0.16 ml) in THF (1.1 ml) was added dropwise to the mixture. The mixture was stirred for 3 hr at -75°C. The reaction mixture was extracted with ethyl acetate after adding sat NH_4Cl aqueous solution, and the extracts were washed with water, dried on anhydrous Na_2SO_4, evaporated in vacuo to give a residue, which was chromatographed on silicic acid column using benzene-ethyl acetate (9 : 1 v/v) as an eluent to yield pale yellow crystals 14a (396 mg, 80.5 %), m.p.44.2 - 46.2°C, IR (KBr) cm^{-1} 3240, 1720, 1580, ^1H NMR $\delta^{CDCl_3}_{TMS}$ ppm 1.25 (3H, d, J=6.4 Hz, $-CH_3$), 1.40 (3H, t, J=7.1 Hz, $-CH_2CH_3$), 2.26 (3H, s, $Ar-CH_3$), 2.88 (1H, d, J=5.1 Hz, H-C-H), 2.94 (1H, d, J=1.7 Hz, H-C-H), 3.86 (3H, s, $-OCH_3$), 4.38 (2H, q, J=7.1 Hz, OCH_2CH_3 overlapped with -CHOH), 7.42 (1H, br, Ar-H), 7.50 (1H, bs, Ar-H). MS m/z 280 (M^+), 262 (M^+-H_2O), HR-MS m/z 280.1317 (M^+), calc for $C_{15}H_{20}O_5$ 280.1310, (Found: C, 64.20; H, 7.12 %. $C_{12}H_{20}O_5$ requires C, 64.29; H, 7.14 %).

Ethyl 3-(3-hydroxybutyryl)-4-methoxy-2-methylbenzoate (14b)

According to the same procedure in the case of 13a, 13b (910.4 mg) was converted to 14b (819.6 mg, 75.9 %) as a syrup. IR (neat) cm^{-1} 3450, 1710, 1580, ^1H NMR $\delta^{CDCl_3}_{TMS}$ ppm 1.25 (3H, d, J=6.4 Hz, $-CH_3$), 1.38 (3H, t, J=7.1 Hz, $-OCH_2CH_3$), 2.44 (3H, s, $Ar-CH_3$), 2.84 (1H, d, J=3.9 Hz, HCH), 2.90 (1H, d, J=0.7 Hz, HCH), 3.85 (3H, s, OCH_3), 4.33 (2H, q, J=7.1 Hz, OCH_2CH_3 overlapped with -CH-), 6.78 (1H, d, J=8.8 Hz, Ar-H), 7.95 (1H, d, J=8.8 Hz, Ar-H). MS m/z 280 (M^+), 265 (M^+-CH_3), 262 (M^+-H_2O), HR-MS m/z 280.1289 (M^+), calc for $C_{15}H_{20}O_5$ 280.1310. (Found: C, 65.39 % $C_{15}H_{20}O_5$ requires C, 64.29; H, 7.14 %).

Pyrenochaetic acid A (3)

A mixture of 14a (426 mg) and conc HCl (3 ml) was refluxed for 13 hr. After adding water, the reaction mixture was extracted with ethyl acetate and combined extracts were washed with brine, dried on anhydrous Na_2SO_4, concentrated in vacuo to give a residue which was chromatographed on a silicic acid column eluting with benzene-ethyl acetate (5 : 1 v/v) to give white powder, which was recrystallized from chloroform-hexane to yield pyrenochaetic acid, m.p.172.0 - 176.0°C (lit[2] m.p.176 - 179°C). IR (KBr) cm^{-1}: 2950, 1690, 1660, 1580, ^1H NMR $\delta^{CDCl_3}_{TMS}$ ppm 1.94 (3H, d, J=5.1 Hz, CH_3), 2.23 (3H, s, $Ar-CH_3$), 3.84 (3H, s, $-OCH_3$), 6.36 (1H, d, J=16.3 Hz, =CH), 6.56 219 (M^+-CH_3), HR-MS m/z 234.0906 (M^+), calc for $C_{13}H_{14}O_4$ 234.0982.

3-Crotonoyl-4-methoxy-2-methylbenzoic acid (15)

A mixture of 14b (727 mg) and conc HCl (4.6 ml) was refluxed for 17 hr and the reaction mixture was extracted with ethyl acetate. Combined extracts were washed with brine, dried over anhydrous Na_2SO_4, evaporated in vacuo to give a residue, which was chromatographed on silicic acid column using benzene-ethyl acetate (3 : 1 v/v) to yield white powder (223.6 mg). The powder was recrystaled from chloroform to give 15, m.p.157.3 - 161.3°C, IR (KBr) cm^{-1}, 1690, 1590, ^1H NMR $\delta^{CDCl_3}_{TMS}$ ppm 1.93 (3H, d, J=5.3 Hz, =C-CH_3), 2.45 (3H, s, Ar-CH), 3.83 (3H, s, $-OCH_3$), 6.35 (1H, dq, J=15.8 Hz, 5.3 Hz, =CH), 6.83 (1H, d, J=8.8 Hz, Ar-H), 8.13 (1H, d, J=8.8 Hz, Ar-H). MS m/z 234 (M^+), HR-MS m/z 234.0907 (M^+), calc for $C_{13}H_{14}O_4$ 234.0982.

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