1640, 1460, 1380, 1285, 890 cm$^{-1}$.

**(1*E*,3*E*,11*E*)-Cembra-1,3,11-trien-6-one (5).** The cembratriene **5** was isolated as an oil by HPLC (5% EtOAc in isooctane). The extract gave 51 mg (0.8% of the extract) of compound **5**, which showed $[\alpha]_D$ +353° (*c* 0.6, $CHCl_3$) and the following spectral features: HRMS M$^+$, *m/z* obsd 288.2443, $C_{20}H_{32}O$ required 288.2455; low-resolution MS *m/z* (rel intensity) 288 (24), 286 (46), 271 (11), 259 (12), 243 (15), 217 (18), 203 (100), 189 (20), 177 (45), 175 (35), 161 (40), 151 (59); IR (film) 2960, 2920, 1710, 1660, 1460, 1385 cm$^{-1}$; UV (MeOH) 254 nm (ε 28 500), 248 (28 000).

**(1*Z*,3*Z*,11*E*)-Cembra-1,3,11-trien-6-one (6).** The cembratriene **6** was isolated as an oil by HPLC (5% EtOAc in isooctane). The extract gave 10 mg (0.2% of the extract) of compound **6**, which showed $[\alpha]_D$ +23° (*c* 0.1, $CHCl_3$) and the following spectral features: HRMS M$^+$, *m/z* obsd 288.2440, $C_{20}H_{32}O$ required 288.2455; low-resolution MS *m/z* (rel intensity) 288 (25), 245 (4), 227 (3), 177 (3), 165 (3), 151 (4), 136 (97), 121 (100), 108 (22), 93 (77); IR (film) 2960, 2920, 1710, 1660, 1465, 1380 cm$^{-1}$; UV (MeOH) 248 nm (ε 21 000), 245 (21 000).

**(1*E*,3*Z*,11*E*)-Cembra-1,3,11-trien-6-one (7).** The cembratriene **7** was isolated as an oil by HPLC (5% EtOAc in isooctane). The extract yielded 11 mg (0.2% of the extract) of compound **7**, which showed $[\alpha]_D$ +283° (*c* 0.8, $CHCl_3$) and the following spectral features: HRMS M$^+$, *m/z* obsd 288.2467, $C_{20}H_{32}O$ required 288.2455; low-resolution MS *m/z* (rel intensity) 288 (100), 273 (13), 270 (19), 245 (50), 242 (24), 227 (31), 203 (12), 190 (12), 177 (40), 175 (26), 165 (40), 161 (46), 151 (30); IR (film) 2960, 2930, 1705, 1665, 1460, 1440, 1380, 865 cm$^{-1}$; UV (MeOH) 248 nm (ε 20 500), 243 (21 000).

**Irradiation of (1*E*,3*E*,11*E*)-Cembra-1,3,11-trien-6-one (5).** A solution of compound **5** (11.3 mg, 0.04 mmol) in benzene (15 mL) was placed in a covered quartz test tube within 10 cm of a water-cooled photolysis apparatus and irradiated for 3 h with light from a 450-W Hanovia lamp. After evaporating the solvent, separation by HPLC (5% EtOAc in isooctane) gave four compounds: **1** (1.0 mg, 8.8% yield), **5** (2.1 mg, 18.6%), **6** (1.2 mg, 10.6%), **7** (1.3 mg, 15.9%). The $^1$H NMR spectra of these compounds were identical with those from the natural products. Compounds **2-4** were obtained as a mixture (3.7 mg). Chemical shifts of the key protons (signals in the region of δ 2.8-5.8 and signals of high field methyl protons) in the $^1$H NMR spectrum were within ±0.002 ppm of the natural products. The compounds were quantified by integration of signals corresponding to their C-10 protons (δ 3.99 for **2**, 3.82 for **3**, 4.05 for **4**) in the $^1$H NMR spectrum: **2** (0.7 mg, 6.2%), **3** (1.2 mg, 10.6%), **4** (1.8 mg, 15.9%).

**Irradiation of Calyculone D (1).** A solution of **1** (16.0 mg, 0.06 mmol) was dissolved in benzene (15 mL) and irradiated by using the same apparatus and procedure as described for compound **5**. After 8 h, the solvent was evaporated under vacuum and the $^1$H NMR spectrum of the residue was recorded. The spectrum showed signals for only calyculone D, indicating that no reaction had occurred.

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# Cibaric Acid, a New Fatty Acid Derivative Formed Enzymatically in Damaged Fruit Bodies of *Cantharellus cibarius* (Chanterelle)

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The secondary metabolites of both intact and damaged fruit bodies of the edible mushroom *Cantharellus cibarius* have been investigated. The fruit bodies originally contain several fatty acids, one of the most abundant being 14,15-dehydrocrepenyic acid which is present both as a free fatty acid and as the triglyceride. 14,15-Dehydrocrepenyic acid is proposed to be the precursor of a new fatty acid which is formed enzymatically in response to injury to the fruit bodies. The new compound, called cibaric acid (**1a**), was isolated, and the elucidation of its structure by spectroscopic methods is described.

## Introduction

Fruit bodies of *Cantharellus cibarius* Fr. (chanterelles) are among the most popular edible wild mushrooms, at least in the north of Europe. The fruit bodies are common and easily distinguished from toxic species, their taste is palatable, and they are normally not attacked by parasites like insects and snails. Consequently, large amounts are consumed yearly. The question about the nutritive value of fruit bodies of *C. cibarius*, as well as a general concern for the public health, has stimulated several chemical investigations; the major volatile components have been identified[2] and the presence of fats and fatty acids,[3,4] carotenes,[5] and steroids[6] has been reported. Previous investigations of other mushrooms unattractive to parasites have shown that some of them (e.g. *Lactarius vellereus*,[7] *Agaricus xanthoderma*,[8] and *Paxillus atrotomentosus*[9])

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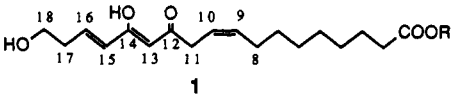
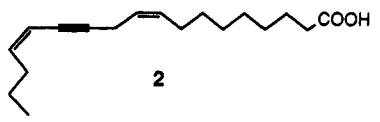
originally do not contain the active and deterring compounds, but form such metabolites enzymatically from less active precursors when the fruit bodies are damaged. We therefore decided to investigate if injury to the fruit bodies initiates the formation of new secondary metabolites also in *C. cibarius*.

## Results and Discussion

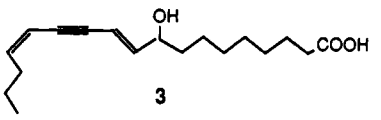
The EtOAc extracts of intact fruit bodies of *C. cibarius* were found to contain large amounts of free fatty acids. The most abundant were isolated and characterized by spectroscopic methods (NMR and MS) and found to be palmitic acid, oleic acid, linoleic acid, and (9*Z*,14*Z*)-9,14-octadecadien-12-ynoic acid (14,15-dehydrocrepenyic acid) **2**. The latter, which previously has been isolated from




**1**




**2**




**3**

a: R=H, b: R=$CH_3$

plants[10] and in very small amounts from cultures of the fungus *Tricholoma grammopodium*,[11] is present both as the free fatty acid and as the triglyceride. It has previously not been reported from *C. cibarius*; however, we propose that it is identical with the polyunsaturated octadecanoic acid derivative previously reported from fruit bodies of this species.[3] The amounts of the polyunsaturated octadecanoic acid described in ref 3 were reported to be 25% of the free fatty acids and 78% of the neutral lipids,[3] which is consistent with the amounts of 14,15-dehydrocrepenyic acid **2** isolated in this investigation. In addition, several of the carotenes and sterols previously reported[5,6] could also be identified. When extracts of intact mushrooms were compared (by TLC) with extracts of specimens that had been ground (to simulate injury) prior to extraction, only one difference was visible. One compound that was not present in intact mushrooms and was not formed chemically in extracts of intact mushrooms (e.g. during standing in room temperature in various solvents for hours, chromatography on $SiO_2$, etc.) was formed in considerable amounts in the response to injury to the fruit bodies. The compound, which we call cibaric acid (**1a**), was isolated and characterized by spectroscopic methods. Cibaric acid is formed slowly and accumulates in the mush up to 15–30 min after the grinding of the mushrooms.

High-resolution mass spectroscopy and NMR spectroscopy established the elemental composition of cibaric acid (**1a**) as $C_{18}H_{28}O_5$, which suggested a fatty acid derivative. NMR data suggested the presence of one carboxylic acid funtionality, which could be transformed to a methyl ester by treatment with diazomethane in ether (forming methyl cibarate, **1b**), one cis and one trans double bond, a keto and an enol functionality, and a primary alcohol function. The stereochemistry of the two double bonds at positions 9 and 15 (9*Z* and 15*E*) was indicated by the coupling constants ($J_{9-10}$ = 10.7 Hz and $J_{15-16}$ = 15.6 Hz) and by NOE NMR experiments. NOE's were observed on 11-H (4%) when 8-H was irradiated, and on 8-H (4%) when 11-H was irradiated. When 16-H was irradiated no NOE was observed on 15-H, but only on 17-$H_2$ (4%) and 18-$H_2$ (5%), while irradiation of 15-H resulted in NOE's on 17-$H_2$ (6%), 18-$H_2$ (5%), and 13-H (10%). The latter indicates that the enolic double bond is *Z*, the isomer which is stabilized by the possibility of an intramolecular hydrogen bond between 12=O and 14-OH.[12] The enol functionality showed typical NMR chemical shifts, a singlet at $\delta$ = 5.52 in the $^1H$ spectrum and a singlet at $\delta$ = 176.8 and a doublet at $\delta$ = 99.2 in the $^{13}C$ spectrum.[13] $^1H$–$^1H$ and $^1H$–$^{13}C$ NMR correlation spectra as well as coupled $^{13}C$ spectra with selective irradiation of pertinent proton frequencies established how these fragments are joined together. Irradiation of $\delta$ = 3.12 (11-$H_2$) transformed the signal of C-12 to a broad singlet while irradiation of $\delta$ = 5.52 (13-H) transformed the same signal to a triplet, irradiation of either $\delta$ = 2.32 (2-$H_2$) or 1.61 (3-$H_2$) transformed C-1 to a triplet, and irradiation of either $\delta$ = 6.81 (16-H), 5.61 (15-H), or 5.52 (13-H) transformed C-14 to a triplet. The conjugation of the $\beta$-diketone with the 15,16 double bond stabilizes the enol tautomer with the keto function on C-12 and also explains the observed UV absorption maximum at 308 nm[14] and the shift of the hydroxy (extending to below 2800 $cm^{-1}$) and carbonyl (at 1530 $cm^{-1}$) IR frequencies.[15] In both the $^1H$ and $^{13}C$ NMR spectra small signals appropriate to the keto tautomer of **1a** were observed, and the enol/keto ratio in $CDCl_3$ could, from the integrals in the $^1H$ NMR spectrum, be estimated to 20. The keto–enol tautomerization rate was low; during a $^1H$ NMR experiment in $CD_3OD$ the signal for 13-H disappeared slowly and was completely gone first after several hours at room temperature. No signals for individual OH protons were visible in the $^1H$ NMR spectrum.

It is reasonable to believe that 14,15-dehydrocrepenyic acid, **2**, formed by dehydrogenation of stearic acid via oleic acid, linoleic acid, and crepenyic acid,[11] is the biogenetic precursor of cibaric acid, **1a**, although this should be demonstrated by feeding experiments with labeled compounds. When 14,15-dehydrocrepenyic acid, **2** (as a free fatty acid or as the triglyceride), was left for months at −25 °C either neat or in a $CDCl_3$ solution, it was oxidized to (10*E*,14*Z*)-9-hydroxy-10,14-octadecadien-12-ynoic acid (**3**). Compound **3**, which has not been reported previously, was never observed in freshly prepared extracts of *C. cibarius*.

Nothing is presently known about whether cibaric acid (**1a**) possess any significant biological activity, e.g. insect antifeedant activity, or if it poses a hazard to consumers of wild mushrooms. Other hydroxylated polyunsaturated fatty acids have been shown to possess potent activities and have for instance been proposed to be self-defensive substances in rice plants against rice blast disease.[16] We

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**Table I. $^{13}C$ NMR Data of Cibaric Acid (1a) and 9-Hydroxy-10,14-octadecadien-12-ynoic Acid (3) (76 MHz, $CDCl_3$)[a-c]**

| | 1a | | | 3 | |
|---|---|---|---|---|---|
| C | δ | mult | J, Hz | δ | mult |
| 1 | 179.1 | stt | 6, 4 | 179.7 | s |
| 2 | 34.0 | tm | 132 | 33.9 | t |
| 3 | 24.6 | tm | 127 | 24.6 | t |
| 4 | 28.9[a] | tm | - | 28.9[b] | t |
| 5 | 29.0[a] | tm | - | 29.0[b] | t |
| 6 | 29.0[a] | tm | - | 29.2[b] | t |
| 7 | 29.2[a] | tm | - | 25.1 | t |
| 8 | 27.3 | tm | - | 32.2 | t |
| 8 | 134.0 | dt | 152, 5 | 86.2 | d |
| 10 | 121.5 | dtt | 159, 7, 5 | 140.6 | d |
| 11 | 38.8 | tdd | 127, 9, 4 | 114.3 | d |
| 12 | 199.3 | sdt | 8, 5 | 91.0[c] | s |
| 13 | 99.2 | d | 164 | 88.0[c] | s |
| 14 | 176.8 | sddd | 5, 5, 5 | 108.9 | d |
| 15 | 127.9 | dm | 156 | 144.5 | d |
| 16 | 140.2 | dtt | 156, 6, 5 | 32.4 | t |
| 17 | 35.8 | tm | 132 | 22.1 | t |
| 18 | 61.1 | tdt | 144, 5, 3 | 13.7 | q |

[a-c] Interchangeable.

hope to have some results concerning the activities of cibaric acid **1a** shortly.

## Experimental Section

Fruit bodies of *C. cibarius* were collected in the vicinity of Lund, in the county of Värmland in Sweden, and also purchased at the local market in Lund (with Poland as the stated origin). Ethyl acetate extracts were prepared both of the intact mushrooms and of specimens that had been injured for 15–30 (typically 20) min. Injury to the fruit bodies was simulated by grinding them at room temperature in an ordinary meat grinder. No differences (by TLC) between extracts prepared from mushrooms collected at different sites were noted. TLC analyses were made on $SiO_2$ plates developed with ethyl acetate/heptane and ethyl acetate/heptane/methanol mixtures and visualized by spraying with anisaldehyde/sulfuric acid and warming to 120 °C. The melting point for compound **1a** is not corrected.

**(9*Z*,13*Z*,15*E*)-14,18-Dihydroxy-12-keto-9,13,15-octadecatrienoic acid (1a)** (cibaric acid, approximately 0.01% of fruit bodies of *C. cibarius* that were ground 20 min prior to extraction) was obtained as a white solid by chromatography on $SiO_2$ and recrystallization in ethyl acetate: mp 69.5–70.5 °C; MS [EI 70 eV *m/z* (% rel int)] 324.1950 ($M^+$), $C_{18}H_{28}O_5$ requires 324.1937 (39), 306 (31), 294 (18), 279 (73), 261 (40), 167 (98), 149 (80), 141 (100), 123 (73), 99 (88), 81 (90); $^1H$ NMR (300 MHz, $CDCl_3$) 6.81 (dt, C(16)H, $J_{15-16}$ = 15.6, $J_{16-17}$ = 7.2), 5.94 (ddt, C(15)H, $J_{15-16}$ = 15.6, $J_{15-17}$ = 1.4), 5.61 (dtt, C(9) H, $J_{8-}J_9$ = 7.1, $J_{9-10}$ = 10.7, $J_{9-11}$ 1.2), 5.52 (s, C(13)H), 5.50 (dtt, C(10)H, $J_{8-10}$ = 1.3, $J_{9-10}$ = 10.7, $J_{10-11}$ = 7.1), 3.77 (t, C(18)$H_2$, $J_{17-18}$ = 6.3, 3.12 (ddt, C(11)$H_2$, $J_{8-11}$ = 1.5, $J_{9-11}$ = 1.2, $J_{10-11}$ = 7.1), 2.48 (ddt, C(17)$H_2$, $J_{15-17}$ = 1.4, $J_{16-17}$ = 7.2, $J_{17-18}$ = 6.3), 2.32 (t, C(2)$H_2$, $J_{2-3}$ = 7.4), 2.04 (ddtt, C(8)$H_2$, $J_{7-8}$ = 6.7, $J_{8-9}$ = 7.1, $J_{8-10}$ = 1.3, $J_{8-11}$ = 1.5), 1.61 (m, C(3)$H_2$), 1.40–1.25 (m, C(4)$H_2$, C(5)$H_2$, C(6)$H_2$, and C(7)$H_2$); $^{13}C$ NMR, see Table I; IR (KBr): 3500, 3400, 3200–2800 (very broad), 3100, 1780, 1750, 1690, 1530, 1150 $cm^{-1}$; UV [ethanol (log ε)] 237 (3.81), 308 nm (4.28). Anal. Found: C, 66.63; H, 8.66. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70.

**(9*Z*,13*Z*,15*E*)-14,18-Dihydroxy-12-keto-9,13,15-octadecatrienoic acid methyl ester (1b)** was obtained in a quantitative yield by methylation of cibaric acid (**1a**) with diazomethane in diethyl ether: MS [EI 70 eV *m/z* (% rel int)] 338 ($M^+$) (19), 320 (18), 293 (98), 261 (83), 167 (95), 149 (39), 141 (82), 123 (100), 99 (82); $^1H$ NMR (300 MHz, $CDCl_3$) 6.83 (dt, C(16)H, $J_{15-16}$ = 15.6, $J_{16-17}$ = 7.2), 5.95 (ddt, C(15)H, $J_{15-16}$ = 15.6, $J_{15-17}$ = 1.4), 5.62 (dtt, C(9)H, $J_{8-9}$ = 7.1, $J_{9-10}$ = 10.7, $J_{9-11}$ = 1.2), 5.52 (s, C(13)H), 5.50 (dtt, C(10)H, $J_{8-10}$ = 1.3, $J_{9-10}$ = 10.7, $J_{10-11}$ = 7.1), 3.78 (t, C(18)$H_2$, $J_{17-18}$ = 6.3), 3.66 (s, $OCH_3$), 3.12 (d, C(11)$H_2$, $J_{10-11}$ = 7), 2.49 (ddt, C(17)$H_2$, $J_{15-17}$ = 1.4, $J_{16-17}$ = 7.2, $J_{17-18}$ = 6.3), 2.30 (t, C(2)$H_2$, $J_{2-3}$ = 7.4), 2.05 (dd, C(8)$H_2$, $J_{7-8}$ = 6.7, $J_{8-9}$ = 7.1), 1.60 (m, C(3)$H_2$), 1.40–1.20 (m, C(4)$H_2$, C(5)$H_2$, C(6)$H_2$, and C(7)$H_2$); $^{13}C$ NMR (76 MHz, $CDCl_3$) 199.3 C(12), 176.6 C(14), 174.3 C(1), 140.0 C(16), 134.0 C(9), 128.0 C(15), 121.4 C(10), 99.2 C(13), 61.2 C(18), 51.5 $OCH_3$, 38.8 C(11), 35.9 C(17), 34.1 C(2), 29.3, 29.1, and 29.0 C(4), C(5), C(6), and C(7), 27.4 C(8), 24.9 C(3).

**(10*E*,14*Z*)-9-Hydroxy-10,14-octadecadien-12-ynoic acid (3)** was formed by the autooxidation of dehydrocrepenynic acid **2a** at −25 °C, either neat or in a $CDCl_3$ solution. It was obtained as a colorless oil after $SiO_2$ chromatography: MS [EI 70 eV *m/z* (% rel int)] 291.1960 ($M^+ - 1$), $C_{18}H_{27}O_3$ requires 291.1960 (100), 275 (18), 117 (50), 105 (36), 91 (56), 81 (46), 55 (61), 40 (75); $^1H$ NMR (300 MHz, $CDCl_3$) 6.02 (dd, C(10)H, $J_{9-10}$ = 7.5, $J_{10-11}$ = 16.0), 5.93 (dt, C(15)H, $J_{14-15}$ = 10.9, $J_{15-16}$ = 7.5), 5.91 (dd, C(11)H, $J_{10-11}$ = 16.0, $J_{11-14}$ = 2), 5.58 (ddd, C(14)H, $J_{11-14}$ = 2, $J_{14-15}$ = 10.9, $J_{14-16}$ = 1.0), 4.36 (dt, C(9)H, $J_{8-9}$ = 6, $J_{9-10}$ = 6), 2.34 (t, C(2)$H_2$, $J_{2-3}$ = 7.5), 2.29 (ddt, C(16)$H_2$, $J_{14-16}$ = 1.0, $J_{15-16}$ = 8, $J_{16-17}$ = 8, 1.62 (m, C(3)$H_2$ and C(8)Ha), 1.5 (m, C(8)Hb), 1.44 (tq, C(17)$H_2$, $J_{16-17}$ = 7.4, $J_{17-18}$ = 7.2), 1.40–1.25 (m, C(4)$H_2$, C(5)$H_2$, C(6)$H_2$, and C(7)$H_2$), 0.92 (t, C(18)$H_3$, $J_{17-18}$ = 7.3); $^{13}C$ NMR, see Table I; IR (KBr) 3600, 3110, 1800, 1050, 820 $cm^{-1}$; UV [ethanol (log ε)] 264 (4.13), 278 nm (4.04).

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**Registry No.** **1a**, 130523-93-2; **1b**, 130523-95-4; **2**, 4154-44-3; **3**, 130523-94-3.