Structure and synthesis of a new cyclopentenone derivative from *Trichoderma album*

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A dextrorotatory product isolated from cultures of *Trichoderma album* has been identified as 5-hydroxy-3-methoxy-5-vinyl-2-cyclopenten-1-one, and a synthesis of the latter in racemic form is described. The possibility that this compound might be an artifact produced during the isolation procedure, rather than a true metabolite, is not excluded.

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Un produit dextrogyre isolé des cultures du *Trichoderma album* s'avère etre l'hydroxy-5 méthoxy-3 vinyl-5 cyclopent-2 èn-1 one et on décrit la synthèse de celui-ci sous forme racémique. On n'a pas éliminé la possibilité que ce composé soit un artefact produit au cours d'isolement au lieu d'un vrai métabolite.

Trichoderma album, in plate culture, exhibits antagonism to a variety of microorganisms.[2] This prompted us to examine products extracted from the filtrates after growth of *T. album* in liquid-shake culture. From chromatography of extracted material, we have obtained, in low yield, a new optically active cyclopentenone derivative, $C_8H_{10}O_3$, the structure determination and synthesis of which are described herein.

The compound displays ir absorption ($CHCl_3$) at 1700 and 1592 cm^{-1} (strong), and a uv chromophore $\lambda_{max}(CH_3OH)$ at 243 nm (ε 15 600). These features, together with nmr signals corresponding to an olefinic hydrogen at δ 5.36 (poorly resolved doublet, $J \sim 1.5$ Hz), and methyl ether protons at δ 3.95 (3H, s) are readily interpreted in terms of a 3-methoxy-2-cyclopenten-1-one system (1–3). Infrared absorption at 3555 cm^{-1} indicates the presence of hydroxyl functionality: the latter is further manifested as an exchangeable one-proton signal at δ 3.19 in the nmr spectrum. A three-proton multiplet at δ 5.14–6.20 resembles closely the 11-peak pattern displayed by the vinyl hydrogens of 3-methyl-1-buten-3-ol (4), and the presence of a (tertiary) vinyl carbinol system can accordingly be inferred. The base peak in the mass spectrum, at m/e 55, corresponding to the ion $(C_3H_3O)^+$ provides support for this structural feature.

The combined spectral data can be accommodated by either of the isomeric structures **1** or **2**. (The geminal protons on the ring appear in the nmr spectrum as a two-proton doublet at δ 2.83 ($J \sim 1.5$ Hz).)

The remaining structural ambiguity was resolved by synthesis. Structure **2** was selected as the initial synthetic target since it appeared that it should be accessible by reaction of the known compound **3** with a vinyl Grignard reagent. Accordingly, **3** was prepared (5, 6), via 1,2,4-cyclopentane trione **4** (7), from diethyl acetonedicarboxylate and diethyl oxalate. Reaction of **3** with vinyl magnesium bromide in tetrahydrofuran (8) afforded a complex mixture of products, possibly as a result of anion formation at C-5 (5). The desired product **2** was, however, obtained in 32% yield (not optimized) on changing the solvent to ether, in which both reactants were but sparingly soluble.[3] That the compound obtained from the *T. album* fermentation was not **2** was immediately obvious on

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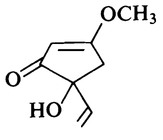
[2] J. L. Ricard: personal communication. We thank Dr. Ricard for providing a culture of *T. album*.

[3] The Grignard reagent was prepared in tetrahydrofuran in the normal manner (8): it was suspended in anhydrous ether after removal of the former solvent (nitrogen stream).



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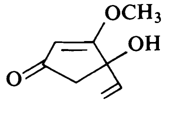

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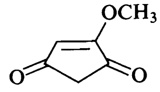

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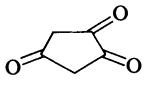

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comparison of their spectra (see Experimental). Thus, for example, though the nmr spectra showed some similarities, significant differences were evident in the signals corresponding to the C-2 vinyl proton, and the methylene protons (for **2**, *singlets* at δ 5.33 and 2.68 ppm, respectively).

While **3**, derived from the more favorable enolic form of **4**, is the sole product (80%) reported from acid-catalyzed reaction of the latter with methanol (6), it appeared that similar treatment of **2** might give rise to an equilibrium mixture containing both **1** and **2**. In the event, when **2** was set aside at ambient temperature in methanol solution containing a catalytic quantity of sulfuric acid, tlc analysis revealed the gradual formation of a second, more polar product. After 4 h, 69 mg of **2** and 45 mg of **1** were recovered, starting from 150 mg of the former.

Comparison of solution spectra and tlc behavior of synthetic **1** thus prepared, with those of the *T. album* product established their identity. A biosynthetic pathway to **1** might comprise cyclization of a tetraketide precursor to a six-membered (orsellinic acid-type) intermediate, with subsequent loss of carboxyl, oxidation, and ring contraction.

The possibility that **1** could be an artifact produced from a metabolite during the isolation procedure was considered, on comparing its chromatographic characteristics with those of the crude extracts from which it was obtained. Since production of **1** has not been observed in subsequent fermentations, we have, as yet, no further evidence relating to the question of its authenticity as a 'true natural product'.

Bioassays, using the disc method, showed that **1** was devoid of antifungal activity against test organisms sensitive to the crude *T. album* extracts.

Experimental

Melting points were determined on a hot-stage apparatus and are uncorrected. Infrared and ultraviolet spectra were recorded on a Beckman Acculab 2 and a Perkin-Elmer 402 spectrophotometer, respectively. Nuclear magnetic resonance spectra were obtained for solutions in deuterochloroform using a Varian T-60 intrument, with tetramethylsilane as internal standard. Preparative thin layer chromatography was carried out on 0.5 mm layers of silica gel GF-254 (E. Merck); bands were detected by viewing under uv light (254 nm).

Isolation of 5-Hydroxy-3-methoxy-5-vinyl-2-cyclopenten-1-one, 1

Material extracted with chloroform from filtered culture medium[4] that had supported growth of *T. album* (liquid shake culture, temperature *ca.* 15°C) for 3 weeks, was passed through a short column of silica gel using chloroform as eluent. After removal of solvent *in vacuo*, the residue was chromatographed on preparative layer plates of silica gel (benzene–acetone, 4:1). A distinct band at R_F *ca.* 0.5 was isolated by extraction with methanol. On rechromatography using the same system, the principal band appeared to have shifted to lower R_F (artifact?). The yield of crystalline product, **1**, obtained from this band was less than 1 mg per litre culture medium. After crystallization from ether–*n*-hexane, **1** was sublimed at 0.1 Torr to give colorless crystals, mp 75–77°C; $[\alpha]_D$ +63° (*c* 0.741 g/100 ml methanol); cd (7.433 × 10^{-4} *M* in methanol, 1 mm cell) λ nm (Δε): 335(0), 281 (+2.36), 263 (0), 238 (+4.32), 219 (0), <219 (negative); ir (KBr) *inter alia* 3400 (br), 3080, 2990, 2940, 2850, 1695, 1575, 1355, 1250, 1190, 1110, and 975 cm^{-1}; ir ($CHCl_3$) 3555, 1700, 1592 (s), and 1362 cm^{-1}; uv λ_{max}(CH_3OH) 243 nm (ε 15 600); nmr spectrum described in text; ms (peaks of relative abundance greater than 20%) *m/e* 154.0631 (73) (calcd. for $C_8H_{10}O_3$: 154.0630), 125(48), 98(34), 97(26), and 55(100).

Preparation of 4-Hydroxy-3-methoxy-4-vinyl-2-cyclopenten-1-one, 2

Vinylmagnesium bromide was prepared in anhydrous tetrahydrofuran from magnesium turnings (300 mg; 12.3 × 10^{-3} g-atom) in the usual manner (8). The solvent was then removed with the aid of a stream of dry nitrogen, and the solid residue was suspended in anhydrous ether (50 ml). To the stirred suspension of vinyl Grignard reagent (ambient temperature, nitrogen atmosphere) was added in several portions from a dropping funnel, 2-methoxy-2-cyclopentene-1,4-dione, **3**, (1 g, 7.93 mmol) (5–7) suspended in ether (20 ml). The mixture was stirred under the same conditions for 4 h, after which saturated ammonium chloride solution was added. The material obtained on work-up (extraction with ethyl acetate etc.) was subjected to chromatography on preparative layer plates of silica gel (benzene–acetone 7:3), affording 98 mg of the cyclopentenedione starting material and 387 mg (32%) of **2**.

The product, **2**, was a colorless gum, ir (neat film) *inter alia* 3380 (br), 3100, 3020, 2990, 2950, 2850, 1690, 1600, 1332, 1252, 1206, and 1171 cm^{-1}; uv λ_{max}(CH_3OH) 238 nm; nmr δ 2.68 (2H, s), 3.73 (1H, br, exchangeable) 3.90 (3H, s), 5.33 (1H, s), and 5.14–6.23 (3H, m, *cf.* ref. 4); ms (peaks of relative abundance greater than 20%) *m/e*

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[4] The culture medium was the basal synthetic medium of Jennison *et al.* (9), but with sucrose as carbon source. Nitrogen was provided by L-glutamic acid.

154.0626(79) (calcd. for $C_8H_{10}O_3$: 154.0630), 127(28), 125(24), 109(57), 108(25), 97(23), 96(87), 95(29), 57(25), and 55(100).

*5-Hydroxy-3-methoxy-5-vinyl-2-cyclopenten-1-one, **1**, Synthetic*

The cyclopentenone vinyl carbinol, **2**, (150 mg, 0.97 mmol) was dissolved in anhydrous methanol (30 ml), and concentrated sulfuric acid (2 drops) was added. The pale yellow solution was stirred at 21°C for 4 h. It was then poured into dilute sodium carbonate solution, and extracted thoroughly with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate, and evaporated. Preparative layer chromatography of the residue on silica gel plates (benzene–acetone, 7:3) afforded starting material, **2**, (69 mg) and the isomer **1** (45 mg). After recrystallization from ether–*n*-hexane, **1** was obtained as colorless crystals, mp 65–67°C; ir ($CHCl_3$), uv (CH_3OH), and nmr ($CDCl_3$) spectra, as well as tlc behavior identical with those of the *Trichoderma* product; ir (KBr) *inter alia*, 3360 (br), 3100, 3025, 3005, 2980, 2950, 2850, 1680, 1575, 1355, 1250, 1195, 1150, 975, and 815 cm^{-1}; ms, *m*/*e* 154.0622; calcd. for $C_8H_{10}O_3$, 154.0630.

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Erratum: Synthesis and characterization of Cu(I) complex compounds with methyl isonicotinate

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In Table 1, the elements for which analyses are given should be in the order Cu, X, C, H, N.