THE TOTAL SYNTHESIS OF MOLLICELLIN A

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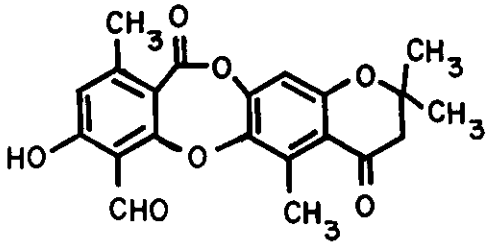
Dedicated to Professor Tetsuo Nozoe on the occasion of his 77th birthday.

The total synthesis of mollicellin A is reported.

The fungus Chaetomium mollicellum, strain MIT M-37, collected from contaminated food produces eight new, structurally related depsidones which we have named mollicellins A-F.[2] The structures of mollicellins A (1) and B (2) were established by X-ray crystallography, while mollicellins D (5), G (3) and H (4) were correlated with A (1) and B (2) by chemical transformations. The remaining three mollicellins, C (6), E (7) and F (8) belong to the same structural series but a correlation with either mollicellin A (1) or B (2) remains to be accomplished and the three structures presented are arbitrary. All eight metabolites are toxic and mollicellins C (6) and E (7) were found to be mutagenic, without enzymic activation in Salmonella typhimurium.[3]

In this communication we report a total synthesis of mollicellin A (1). The synthetic plan called for the preparation of a suitably functionalized diphenyl ether, which could then be cyclized to a depsidone.[4] The readily available diketoester 9[5] served as starting material and on treatment with methanol-benzene in the presence of p-toluenesulfonic acid it gave the vinyl ether 10.[6] When exposed to excess oxalyl bromide in chloroform and then to water ketone 10 yielded a 4:1 mixture of isomeric β-bromoenones separable by chromatography. To establish their structures each isomer



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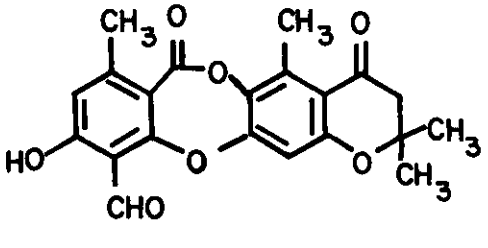

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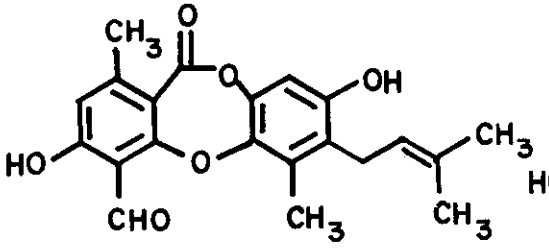

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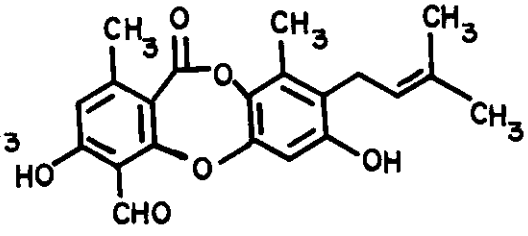

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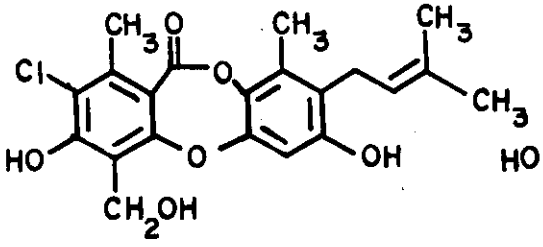

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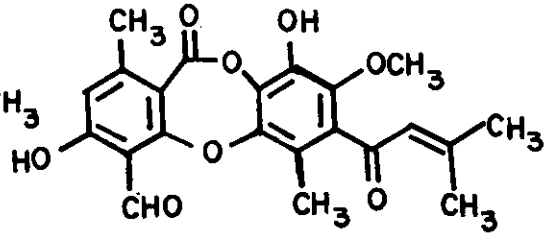

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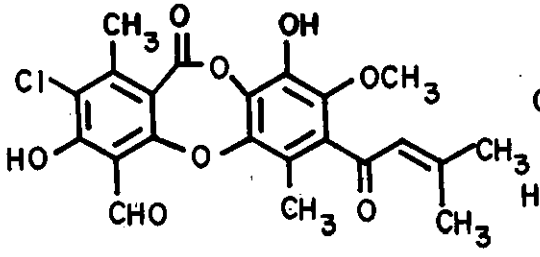

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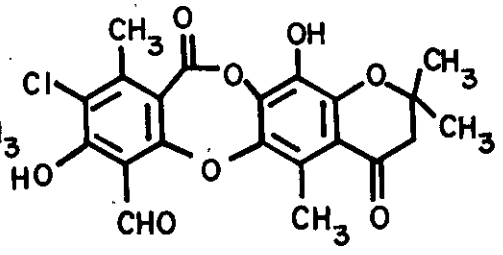

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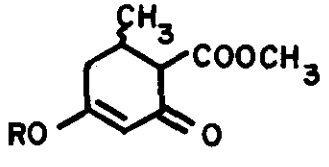
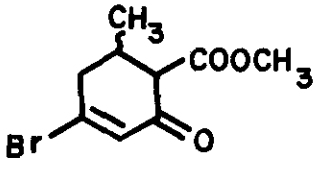
was converted to its aromatic counterpart (13 and 14) by consecutive treatment with (a) phenyltrimethylammonium perbromide in tetrahydrofuran, (b) 1,5-diazabicyclo[5.4.0] undecene in benzene, and (c) methyl iodide in dimethylformamide with suspended potassium carbonate. The aromatic bromide resulting from the major isomer 12 was identical with compound 14 of established structure.[5] In preparative runs the isomeric bromides 11 and 12 were not separated and the crude mixture was condensed with excess N,N-dimethylformamide dimethylacetal at 50° overnight. The resulting dimethylamino-methylene ketone 15 with uv absorption (EtOH) at 354 nm (ε 12,500) had to be purified by chromatography and was obtained in 20% overall yield from starting material 9. Dehydrogenation with o-chloranil in ether at room temperature followed by filtration through a pad of silica gel afforded 16, mp 44-46°, uv (EtOH) 227 nm (ε 17,700), 274 (11,400), 336 (4,500) in 55% yield.



9 R = H

10 R = CH_3



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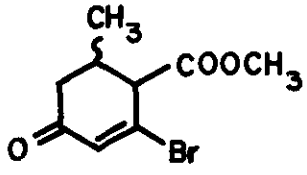

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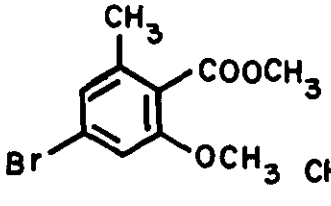

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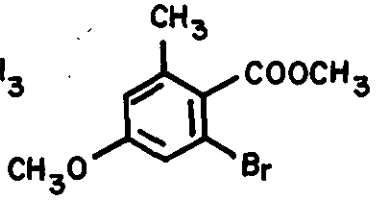

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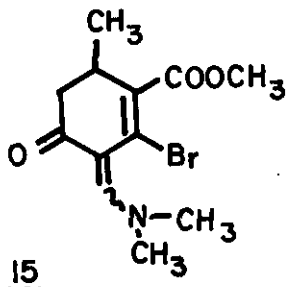

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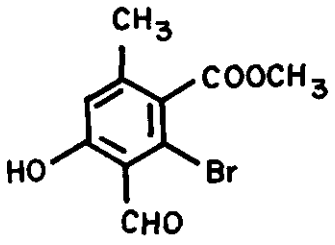

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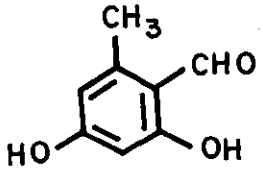

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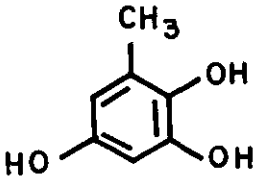

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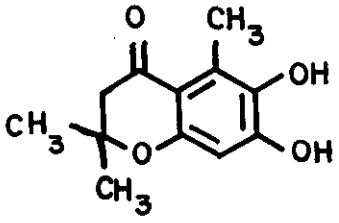

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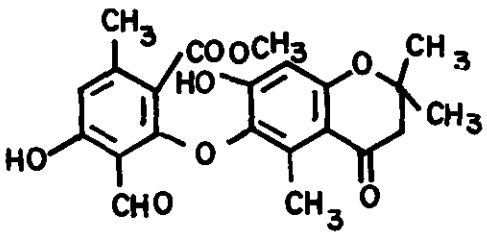
The "right hand" portion of the mollicellin A (1) molecule was synthesized as follows: aldehyde 17,[7] available by formylation of orcinol was oxidized to 2,3,5-trihydroxytoluene (18)[8] mp 147-149° (60%) by the method of Dakin.[9] Conversion to the chromanone 19, mp 216-217°, uv (EtOH) 241 nm (ε 15,000), 282 (13,800), 345 (5700), ir ($CHCl_3$) 1665 cm^{-1} (66%) was accomplished by condensation of 18 with β,β-dimethylacrylic acid and phosphorus oxychloride in the presence of one equivalent of zinc chloride.[10] Spectral data quoted, and others as well, left no doubt that the chromanone had structure 19. The diphenyl ether synthesis of Whitesides[11] using 0.1 M methyl copper in pyridine at -5° C and then at 50° C overnight was used to prepare intermediate 20 (30%) mp 207-209° C, uv (EtOH) 226 nm (ε 28,000), 236 (27,200) 277 (25,000), 332 (8,800). Ester 20 was identical with the compound obtained by



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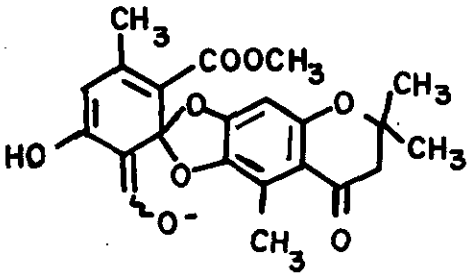

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methanolysis of either mollicellin A (1) or B (2) in the presence of a catalytic amount of sodium hydroxide. In the course of structural work[2] we have shown that the methanolysis of mollicellin B (2) is accompanied by a Smiles rearrangement. It most probably proceeds through intermediate 21 and leads from a m-hydroxyacetophenone to the more extensively delocalized p-hydroxyacetophenone 20. Ester 20 on cyclization in refluxing xylene in the presence of some p-toluenesulfonic acid afforded mollicellin A (1), (25 %) mp 170-171° identical with natural material as judged by ir, uv and proton nmr spectra as well as mixture melting comparisons.

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