Synthesis of the Antibiotic Isopentenynyl Hydroquinones Frustulosin and Frustulosinol

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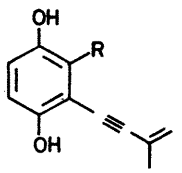
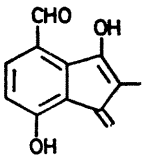
Summary The structures of the title compounds, metabolites from cultures of the fungus *Stereum frustulosum*, have been authenticated by unambiguous total synthesis.

FRUSTULOSIN (**1**) and frustulosinol (**2**) are metabolites of the fungus *Stereum frustulosum* and are active as antibiotics.[1,2] Frustulosin was originally assigned the benzofulvene



(1) R = CHO
(2) R = CH_2OH

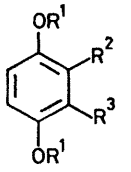


(3)

structure[1] (3), but after the isolation and detailed study of frustulosinol (2) this was revised to (1).[2] The biological activity of (1) combined with the lack of certainty concerning its structure prompted the synthesis now reported (Scheme).

mixture of the *E* and *Z* isomers of the vinyl chloride (9) [overall yield from (7) was 58%; the silylation was necessary to enable chromatographic separation of the product from triphenylphosphine oxide].

Dehydrochlorination of (9) was accompanied by extensive cleavage of the silyl ether grouping and re-silylation[6] was necessary to secure a good yield (77%) of the acetylene (10). The lithium alkynide derived from (10) underwent addition to acetone (74% yield) and the resulting alcohol was dehydrated to afford the enyne (11). Selective removal of the silyl protecting group[6] followed by oxidation gave the aldehyde (12) which was converted into (1) with aqueous acid. The material so obtained was identical (t.l.c.; ^{1}H n.m.r., i.r., and u.v. spectral data; mass spectrometric fragmentation) with natural frustulosin.



MEM = $CH_2OCH_2CH_2OMe$

(4) R^1=H, R^2=R^3=CN —i→ (5) R^1 = MEM, R^2 = R^3=CN

(5) —ii→ (6) R^1 = MEM, R^2,R^3 = $-CO_2CO-$

(6) —iii→ (7) R^1 = MEM, R^2 = R^3 = CH_2OH

(7) —iv→ (8) R^1 = MEM, R^2,R^3 = $-CH_2OCH(OH)-$

(8) —v→ (9) R^1 = MEM, R^2 = $CH_2OSiBu^tMe_2$, R^3=CH=CHCl

(9) —vi→ (10) R^1 = MEM, R^2=$CH_2OSiBu^tMe_2$, R^3=C≡C–H

(10) —vii→ (11) R^1=MEM, R^2=$CH_2OSiBu^tMe_2$, R^3=C≡C–C(Me)=CH_2

(11) —viii→ (12) R^1=MEM, R^2=CHO, R^3=C≡C–C(Me)=CH_2 —ix→ (1)

SCHEME

Reagents: i, NaH, $MeOCH_2CH_2OCH_2Cl$; ii, a, 15% NaOH, b, Ac_2O; iii, $LiAlH_4$, tetrahydrofuran; iv, MnO_2, CH_2Cl_2–pyridine; v, a, Ph_3P=CHCl, b, Bu^tMe_2SiCl, imidazole, $HCONMe_2$; vi, a, $NaNH_2$, liquid NH_3, b, Bu^tMe_2SiCl, imidazole, $HCONMe_2$; vii, a, nBuLi, Me_2CO, b, $MeSO_2Cl$, pyridine; viii, a, AcOH, H_2O, b, MnO_2, CH_2Cl_2; ix, AcOH, HCl, H_2O.

The phenolic groups of the commercially available dinitrile (4) were protected[3] and the resulting bis(methoxyethoxymethyl) (MEM) ether (5)† was converted into the crystalline anhydride (6) (m.p. 60—61 °C; 72% yield). This was reduced[4] to the diol (7) (85% yield). The selective oxidation of one of the hydroxymethyl groups of (7) succeeded using MnO_2 in CH_2Cl_2–pyridine: the resulting unstable hemiacetal (8) was treated immediately with the appropriate Wittig reagent[5] and then silylated[6] to give a

Since frustulosin (1) has previously been converted into frustulosinol[2] (2) the synthesis outlined above also formally constitutes a total synthesis of (2).

I thank Professor Sir Ewart Jones and Dr. V. Thaller for helpful discussion and Dr. M. S. R. Nair for a sample of natural frustulosin.

(*Received, 25th September* 1978; *Com.* 1030.)

† All new compounds gave satisfactory analytical and spectroscopic data.

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