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Total Synthesis of Frustulosin

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Summary The revised structure of the novel antibiotic frustulosin is confirmed by regioselective total synthesis.

RECENTLY Nair and Anchel[1] reported the isolation of yellow antibiotic substances from cultures of the Basidomycete, *Stereum frustulosum*, that exhibited antimicrobial activity at modest concentrations against a broad spectrum of pathogenic bacteria. From preliminary structural studies a novel benzofulvene structure (**1**) was proposed for one of these compounds which was named frustulosin.

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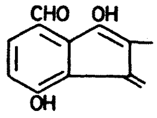
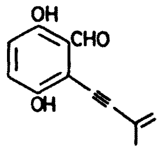
Somewhat later these authors isolated a related substance in much greater quantities and were able to show that the original structure for frustulosin should be revised to a monocyclic acetylenic hydroquinone.[2] We now confirm the revised structure (**2**) for frustulosin by a regioselective total synthesis which incorporates the following novel features: a remote vinyl ether to assist in a regio-directed metallation of an aromatic ring, ethylene iodochloride as a mild and selective iodination reagent, and boron tri-iodide as a selective reagent for ether cleavage in aromatic aldehydes.

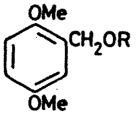
The alcohol (**3a**)† was vinylated under standard conditions with ethyl vinyl ether to afford the vinyl ether (**3b**), b.p. 81—83 °C at 0·05 mmHg.‡ Treatment of a pentane solution of (**3b**) with excess of n-butyl-lithium overnight at 0 °C afforded the lithio-derivative (**4**) as a tan precipitate, which after removal of the solvent was dissolved in ether and treated with 1 equiv. of ethylene iodochloride.[3] After chromatography on silica gel the iodo derivative (**5**) was obtained in 51% yield, m.p. 73—75 °C.



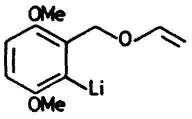
(1)



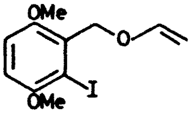
(2)



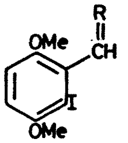
(3) a; R = H
b; R = CH=CH$_2$
c; R = Me$_3$Si
d; R = CH$_2$OMe



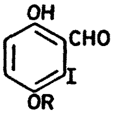
(4)



(5)



(6) R = H, OH
(7) R = O



(8) R = H
(9) R = Me

The regiospecificity of the lithiation can be explained on the basis of co-ordination of the lithium cation with the two proximal oxygen atoms, which appear to activate the aromatic position quite markedly.[4] No other ring metallation products have been observed in > 1% yield as determined by gas chromatography after iodination. Even though the 2-position is activated it must be quite hindered as t-butyl-lithium failed to produce (**4**). Furthermore, polar solvents, complexing agents such as tetramethylethylenediamine, and higher temperatures reduced the formation of (**4**) in favour of metallation at the benzyl position; some benzyl metallation occurs even with n-butyl-lithium in pentane. Metallation of the unprotected alcohol (**3a**) did not proceed past the formation of alkoxide; other alcohol derivatives such as (**3c**) and (**3d**) were cleaved to the alkoxide under the metallation conditions.

The vinyl ether was stable to the metallation conditions, but competed with the carbanion when iodine or other sources of electrophilic iodine were used in the formation of (**5**). Ethylene iodochloride proved to be a much more selective reagent for iodination of (**4**); iodinations were rapid and specific even at room temperature, excess of reagent, b.p. 140 °C, was easily removed, and ethylene and lithium chloride were the only byproducts.

Mild hydrolysis of (**5**) in aqueous acidic tetrahydrofuran afforded the alcohol (**6**), m.p. 108·5—110 °C (CH_2Cl_2–hexane), which was oxidized to the aldehyde with pyridinium chlorochromate in 1 : 1 acetone–CH_2Cl_2. The oxidation was slow, requiring at least 24 h, but there was no over-oxidation. Filtration through silica gel afforded the iodoaldehyde (**7**) in 85% yield, m.p. 113—115 °C (CH_2Cl_2–hexane).

Only boron tri-iodide proved to be a sufficiently mild and selective ether cleavage reagent to effect the transformation of (**7**) to (**8**) in good yield. The presence of both the aldehyde and iodide groups precluded the use of other methods and reagents.[5] Both BBr_3 and trimethylsilyl iodide rapidly attacked the carbonyl group, while powerful nucleophiles resulted in rapid decomposition of the extremely base-sensitive product (**8**). Introduction of the side chain before ether cleavage proved impractical as the acidic reagents induced cyclization with the *ortho* hydroxy group, and furthermore, basic nucleophiles have been shown to cleave readily only one ether unit in a hydroquinone dimethyl ether system.

Treatment of (**7**) with 2 equiv. of BI_3 in CH_2Cl_2 afforded, after quenching with water and filtration through silica gel, a 58% yield of the dihydroxy-iodoaldehyde (**8**) contaminated with a small amount of the monomethoxy-iodoaldehyde (**9**). The dihydroxy compound was readily separated from (**9**) by sublimation below 115 °C at 0·15 mmHg to afford, after recrystallization from CH_2Cl_2–hexane, (**8**), m.p. 148—150 °C.

The iodoaldehyde (**8**) was converted into frustulosin by heating with 2 equiv. of copper(I) isopropenylacetylide[6] in dimethylformamide at 70—90 °C. After 3 h a mixture of starting material, frustulosin, and an as yet unidentified yellow solid which may be a quinone, was obtained. Chromatography on silica gel afforded pure frustulosin, m.p. 136—138 °C, identical in all respects to an authentic sample.

We thank M. S. Nair, New York Botanical Garden, Bronx, New York, for a generous sample of frustulosin.

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† Prepared by hydride reduction of the readily available aldehyde (Aldrich Chemical Co.).

‡ Satisfactory spectral and analytical data were obtained for all compounds reported.

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