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Enantioselective Synthesis of Fusarentin Methyl Ethers: Insecticidal Metabolites of *Fusarium larvarum*

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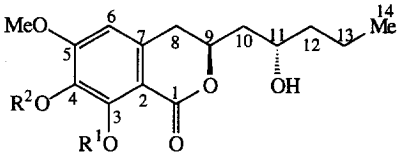
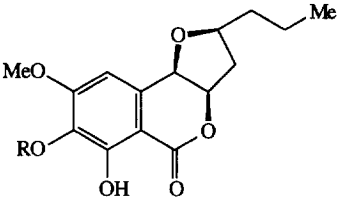
Abstract: *Fusarentin 4,5-dimethyl ether (**1**) and its 4-desmethoxy analogue are synthesised* via *acylation of the benzylic anion of* N,N-*dimethyl-2,3,4,-trimethoxy-6-methylbenzamide (**9**) and* N,N-*dimethyl-2,4-dimethoxy-6-methylbenzamide (**8**) with* N-*methoxy*-N-*methyl-*(S)-*3*-tert-*butyldimethylsilyloxyhexanamide (**13**): subsequent reduction of ketone (**15**) to the* anti-*1,3-diol (**16**) and acid catalysed cyclisation gives (**1**).*

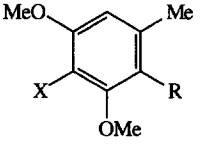
The fusarentin ethers (**1**) - (**3**) were originally isolated along with monocerin (**4**) and its 4-*O*-demethyl analogue (**5**) from *Fusarium larvarum.*[1] Monocerin has been isolated from a number of sources[2,3,4] and the group of metabolites have been shown to exhibit antifungal, insecticidal and phytotoxic properties.



1 $R^1 = H, R^2 = Me$
2 $R^1 = Me, R^2 = H$
3 $R^1 = R^2 = H$

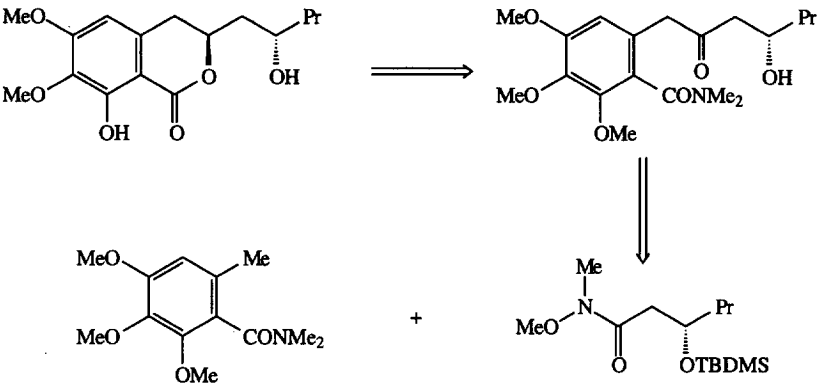


4 R = Me
5 R = H



6 X = H, R = CO_2Et
7 X = OMe, R = CO_2Et
8 X = H, R = $CONMe_2$
9 X = OMe, R = $CONMe_2$

There have been a number of synthetic approaches to this group.[5,6,7] Our previous synthesis[6] of monocerin based on addition of benzylic anions derived from the benzoate (**7**) to (*S*)-3-tetrahydropyranyloxyhexanal suffered from the tendency of the highly reactive anions to self-condense, and gave low stereoselectivity in the addition step. We now report an improved enantioselective synthesis of the fusarentins in which both these problems are overcome and which allows the preparation of putative advanced intermediates proposed to be involved in the later stages of monocerin and fusarentin biosynthesis.[4] The strategy outlined in Scheme 1 is based on the acylation of the benzylic anions[8] derived from the *N,N*-dimethyl-benzamides (**8**) and (**9**) with the Weinreb amide (**13**) followed by diastereoselective reduction of the resulting β-hydroxy ketone.[9,10]

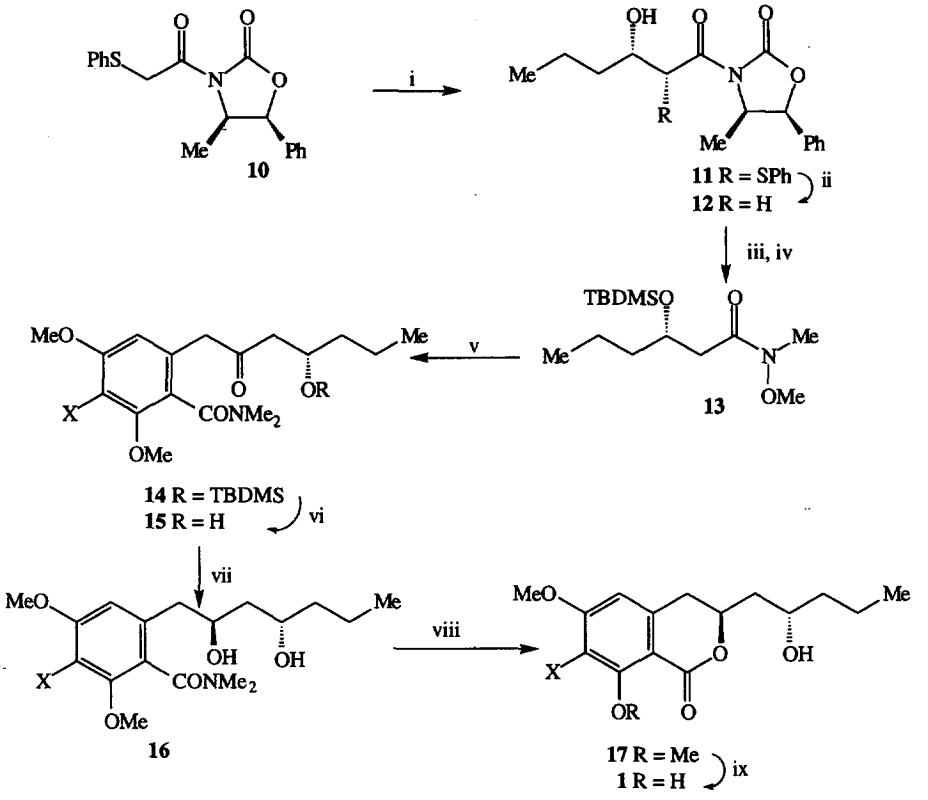


Scheme 1

The Weinreb amide (**13**) was prepared as shown in Scheme 2.[11,12] 2-Thiophenoxyacetic acid, formed quantitatively from reaction of bromoacetic acid with thiophenol[14], was converted to the corresponding acid chloride and acylation of the lithium oxazolidinone derived from norephedrine[15] afforded imide (**10**). Generation of the boron *Z*-enolate and reaction with butanal gave the aldol product (**11**) which was desulphurised to provide (**12**) in 87% e.e. and 63% yield over the two steps.[16] Transammination[17] to the *N*-methoxy-*N*-methyl amide followed by TBDMS protection of the alcohol functionality cleanly provided (**13**) in 89% yield.

The benzamides (**8**) and (**9**) are readily prepared by treatment of the corresponding benzoates[18] with trimethylaluminium and *N,N*-dimethylamine hydrochloride.[19] The anion of benzamide (**9**), generated with *sec*-butyllithium, reacted smoothly with Weinreb amide (**13**) to give ketone (**14**) in 76% yield, with none of the problems associated with the corresponding benzoate-derived anions. Deprotection[20] to (**15**) and reduction[21] with tetramethylammonium triacetoxyborohydride formed the *anti*-diol (**16**) in 92% yield. The NMR spectra of these compounds is complicated by the extra atropisomeric asymmetric centre created by hindered rotation of the benzamido group[22] and so the stereoselectivity of the reduction could not be established at this stage. However, facile acid-catalysed hydrolysis[23] of the benzamide gave the dihydroisocoumarin (**17**) directly in 78% yield.

NMR Analysis of (**17**) indicated that the desired diastereomer was formed in approximately 16:1 ratio with the minor 9-epimer. Selective demethylation with boron trichloride gave fusarentin ether (**1**) in 82% yield to complete the total synthesis. The ^{1}H NMR spectrum, melting point (101-102°C) and optical rotation of the synthetic material ($[\alpha]_D$ = -24°) were in agreement with those of the natural product (m.p. 103°C, $[\alpha]_D$ = -29°).[1] The ether (**1**) has previously been efficiently converted to monocerin in a "biomimetic" cyclisation.[6]



Reagents: i) butanal, Bu_2BOTf, $^iPr_2NEt$; ii) $^nBu_3SnH$, AIBN; iii) MeONHMe.HCl, $AlMe_3$, THF; iv) TBDMSCl, imid., DMF; v) **8** or **9**, *sec*-BuLi, THF; vi) 1% HCl, EtOH; vii) $Me_4N(OAc)_3BH$, AcOH, MeCN, -5 to -10°C; viii) 3M HCl; ix) BCl_3, DCM

Scheme 2. Enantioselective synthesis of fusarentin ethers

Repeating the sequence starting from the dimethoxy analogue (**8**) proceeds in similar fashion to give the 4-desmethoxy-analogue of (**1**) in good yield.

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