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ENANTIOSELECTIVE SYNTHESIS OF MONOCERIN AND FUSARENTIN ETHERS: ANTIFUNGAL AND INSECTICIDAL FUNGAL METABOLITES.

Michael P. Dillon, Thomas J. Simpson* and J.B. Sweeney

**School of Chemistry, University of Bristol,
Cantock's Close, Bristol, BS8 1TS.**

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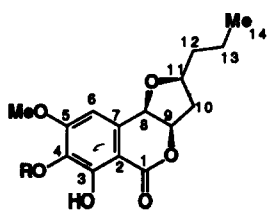
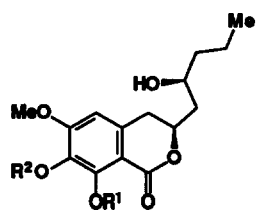
Abstract: Fusarentin 4,5-dimethyl ether (4) is synthesized via *condensation of the benzylic* anion *of ethyl 3,4,5-trimethoxy-6-methylbenzoate (7) with (S)-3-tetrahydropyranyloxyhexanal (8); subsequent biomimetic cyclisation of (4) gives monocerin (I).*

Monocerin (1), its 4-O-demethyl analogue (2) and the fusarentin ethers (3-5) have been isolated from several fungal species and have been shown to exhibit antifungal, insecticidal and phytotoxic activity. [1-5] The



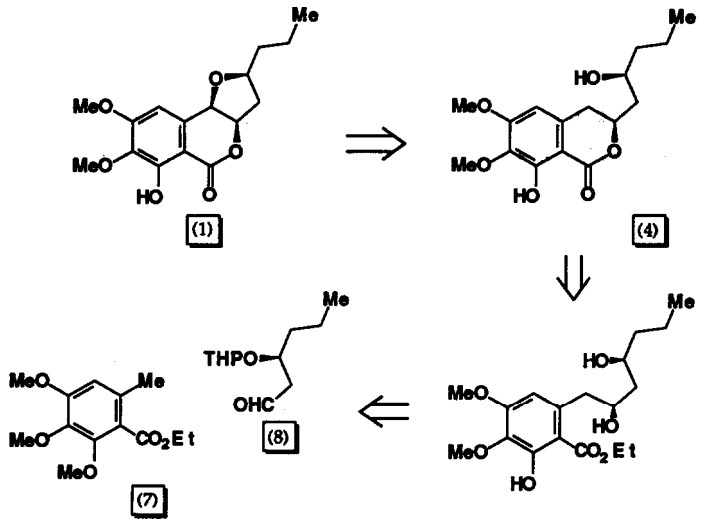
(1) R=Me
(2) R=H



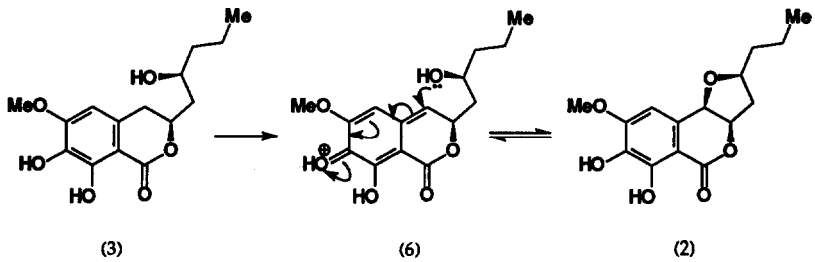
(3) $R^1=R^2=H$
(4) $R^1=H, R^2=Me$
(5) $R^1=Me, R^2=H$

synthesis of fusarentin 4,5-dimethyl ether (4) and its biomimetic cyclisation to provide monocerht is now reported.[6] The general strategy is based on condensation of the benzylic anion derived from ethyl 2,3,4-trimethoxy-6-methylbenzoate (7) with a suitably protected 3-hydroxyhexanal (8) as shown in Scheme 1.

The reuosynthetic analysis is based on the results of biosynthetic studies which were consistent with formation of monocerin via the corresponding fusarentin ether (3) by oxidation to the quinone methide (6).[3] This would allow tetrahydrofuran ring formation by conjugate addition of the 1 1-hydroxyl to C-8 as shown in Scheme 2. The facile formation of (6) by oxidation of (3) or the reversible ring opening of (2) has been suggested to be responsible for the observed biological activities of thii group of metabolites.[7]



Scheme 1. Retrosynthetic analysis of monocerin

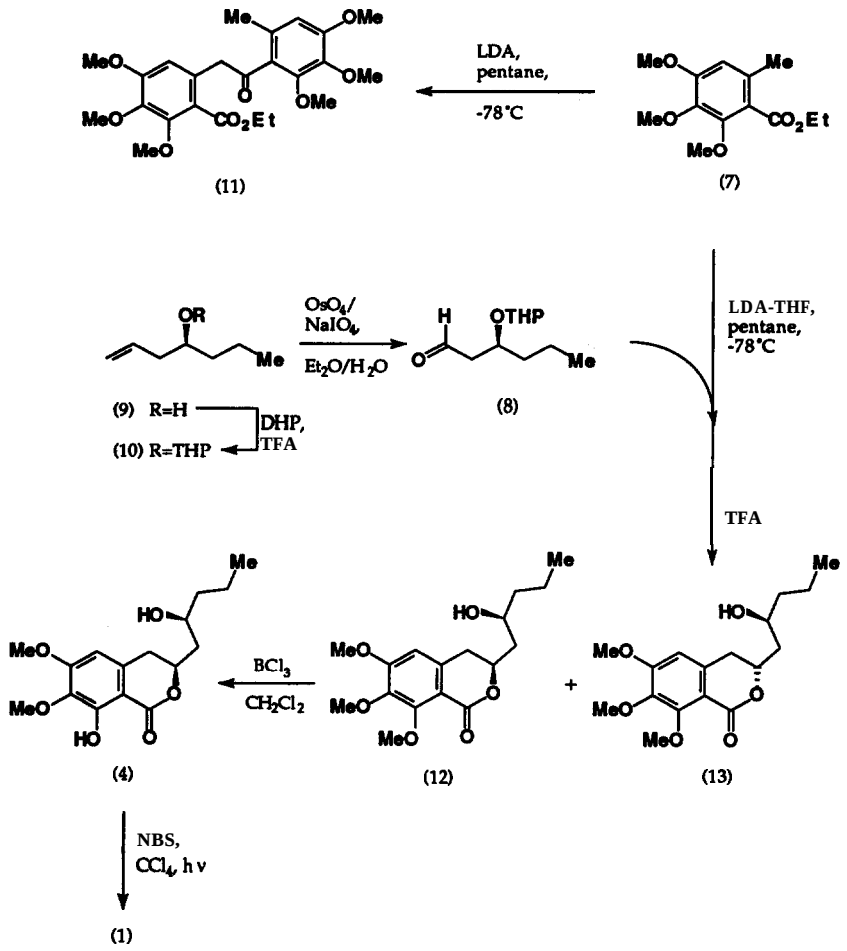


Scheme 2. Proposed interconversion of fusarentin methyl ether and monocerln via a quinone **methide** intermediate

The tetrahydropyranyl ether (8) of **(S)-3-hydroxyhexanal** and the benzoate **(7)** were prepared as shown in Scheme **3.**[8] Brown has **reported**[9] that **B-allylbis(2-isocaranyl)borane** derived from the readily available **(+)-2-carene** will convert aldehydes to homoallylic alcohols with high enantiomeric excess **(e.e.).** Accordingly, treatment of butyraldehyde gave **(S)-hept-1-en-4-ol (9)** in 76% yield (94% **e.e.).**[10] This was converted to the tetrahydropyranyl ether **(10, 98%)** and subsequent cleavage of the olefin using catalytic osmium tetroxide and sodium **metaperiodate**[11] gave the required **(S)-3-tetrahydropyranyloxyhexanal (8, 85%).**

Ethyl **2,3,4-trimethoxy-6-methylbenzoate** (7) was readily prepared by **formylation**[12] of ethyl **2-hydroxy-4-methoxy-6-methylbenzoate** followed by Dakin **oxidation**[13] and methylation. Initial attempts to form the benzylic **anion**[14] using lithium **diisopropylamide (LDA)** in tetrahydrofuran **(THF)** gave no evidence of anion formation. Changing the solvent from THF to pentane gave the ketone (1 **1),** the product of self-condensation of the desired anion as the major product. Formation of the anion in a sufficiently stable

form for condensation with the aldehyde (8) was achieved by generation of LDA in pentane in the presence of one equivalent of THF. Addition of a pentane solution of ethyl **2,3,4-trimethoxy-6-methylbenzoate** (7) at **-78°C** gave a deep-red **coloured** solution, characteristic of anion formation. The benzylic anion was condensed with the aldehyde using a specially constructed **flask**[15] which facilitated transfer of the anionic solution into the solution of the aldehyde at **-78°C**.



Scheme 3. Enantioselective synthesis of the fusarentin ethers and monocerin

After work-up the crude reaction mixture was deprotected to give the dihydroisocoumarin, formed by spontaneous lactonisation of the initial aldol product, in 66% yield as a **2.7:1** mixture of the desired **9(R),11(S)** diastereoisomer (12) and its **9(S),11(S)** epimer (13). These diastereoisomers were separated by multiple elution preparative **t.l.c.** The stereochemistry was **confirmed** by demethylation[16] of (13) to give

fusarentin 4,5-dimethyl ether (4.91%). The ^{1}H NMR spectrum and optical rotation of the synthetic material ($[\alpha]_D = -26.2^{o}$) were in agreement with those of the natural product ($[\alpha]_D = -29^{o}$).[2]

Treatment of fusarentin 4,5-dimethyl ether (4) under Wohl-Ziegler bromination conditions[17] resulted in direct cyclisation of the 1 1-hydroxyl onto the C-8 benzylic position to give monocerin (1) in 70% yield. This showed an optical rotation of ($[\alpha]_D = +50.5^{o}$) compared to that of the isolated natural product ([a], = $+53^{o}$). High field ^{1}H and ^{13}C NMR confirmed the presence of a single diastereoisomer.

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