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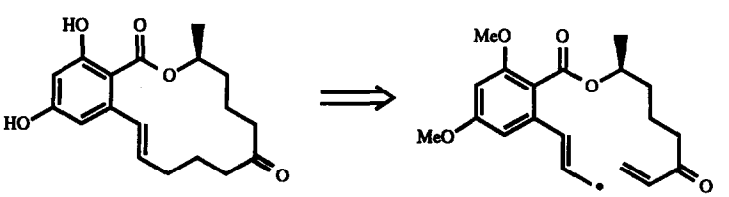
# SYNTHESIS OF MACROCYCLES VIA ALLYLIC RADICAL INTERMEDIATES. A TOTAL SYNTHESIS OF (-)-ZEARALENONE

Stephen A. Hitchcock and Gerald Pattenden*

Department of Chemistry, The University, Nottingham NG7 2RD

Summary: A concise synthesis of optically active (-)-zearalenone (1) which uses a novel 14-endo trig macrocyclisation from an allylic radical intermediate (Scheme 1) as a key feature, is described.

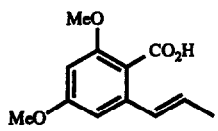
The 14-membered macrolide zearalenone (1) is an oestrogenic mycotoxin produced by various fusaria which colonise maize, barley, oats and wheat.[1] First isolated from the mycelium of the fungus *Gibberella zeae* (*Fusarium graminearum*), zearaleone is just one member of a growing family of biologically important "resorcylic acid lactones" (RAL's) which have been found in nature.[2] Although a number of syntheses of racemic zearalenone have been published,[3] to our knowledge no total synthesis of natural S-zearalenone has been described. In earlier work we have described the use of allylic radical intermediates in macrocyclisation reactions leading to members of the cembranoid family of natural diterpenes.[4] The presence of a δ-unsaturated ketone residue in zearalenone (1) led us to design a new synthetic strategy to the molecule based on the 14-endo-trig cyclisation from the cinnamyl radical intermediate (2) shown in Scheme 1. In this Letter we describe the successful outcome of this idea using the resorcinol derivative (3), and the chiral alcohol (4) derived from naturally occurring parasorbic acid (5), as key intermediates.



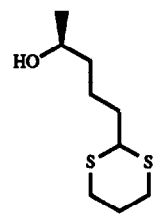

(1) (2)

Scheme 1

Thus, deprotonation of the readily available methyl orsellinate derivative (6a[5]) (LDA, THF, -78°C), followed by sulphenylation of the resulting carbanion using diphenyl disulphide, first led to the phenyl sulphide (6b).[6] Treatment of (6b) with potassium hexamethyldisilazide (THF, -78°C) followed by quenching with iodoethane next produced the substituted sulphide (7; 94%) which on oxidation ($NaIO_4$, MeOH) and thermal elimination ($C_6H_5Me$, Δ, 2h) of phenylsulphenic acid gave rise to the E-alkene (8).[7] Saponification of (8), using KOH-DMSO, then provided the resorcinol derivative (3), m.p. 85-6°C ($Et_2O$-hexane); $\delta_H$ 1.9 (dd, J 6.7 and 1.6 Hz; :CHMe), 3.89 (OMe), 3.92 (OMe), 6.2 (dq, J 15.5 and 6.7 Hz, ArCH:CH), 6.4 (d, J 2.2 Hz, :CH), 6.5 (d, J 2.2 Hz, :CH), 6.8 (dq, J 15.5 and 1.6 Hz, ArCH:CH) p.p.m.




(3)

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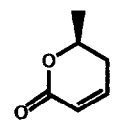


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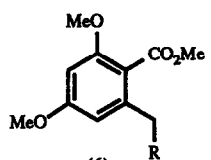
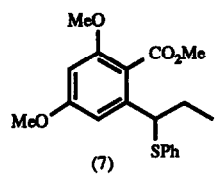
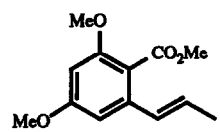



(6)

a. R = H
b. R = SPh




(7)

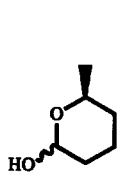



(8)

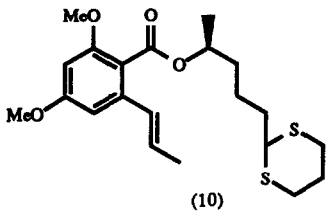
Sequential reduction (*i.e.* $H_2$-Pd/C; then $LiAlH_4$) of naturally derived parasorbic acid (5)[8] led to the cyclic hemi-acetal (9) which was converted to the known dithiane (4)[9] with propanedithiol in the presence of boron trifluoride. Treatment of the carbinol (4) with the acid chloride derived from (3) [$(COCl)_2$ DMF, THF, 25°C] next led to the ester (10) as an oil, $[\alpha]_D$ + 17.6° (c. 1.0, $CHCl_3$); $\nu_{max}$ (film) 1715 $cm.^{-1}$; $\delta_H$ 1.34 (d, J 6.8 Hz, CHMe), 5.2 (m, OCHMe) p.p.m.

Deprotection of (10), using HgO-$HgCl_2$ in aqueous acetonitrile then provided the corresponding aldehyde (54%) which upon treatment with vinylmagnesium bromide (THF, -78°C) led to the allylic alcohol (11; 78%). Oxidation of (11) using

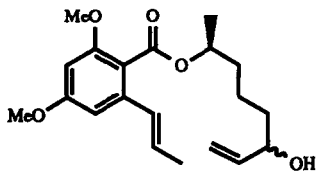
manganese dioxide in dichloromethane finally gave the enone precursor (12), $[\alpha]_D$ + 27.2° (c. 1.1, $CHCl_3$; $\nu_{max}$ (film) 1715 $cm.^{-1}$; $\delta_H$ 1.32 (d, J 6.8 Hz, CHMe), 4.9-5.4 (m, 2H), 5.8 (dd, J 9 and 4 Hz, :CH), 6.0-6.9 (m, 5H) p.p.m. to the radical intermediate shown in Scheme 1.



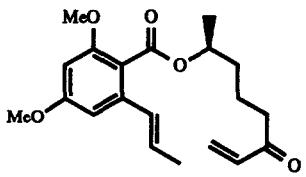

(9)



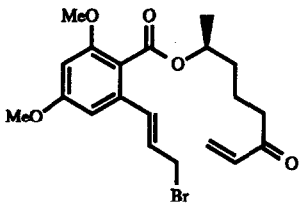

(10)



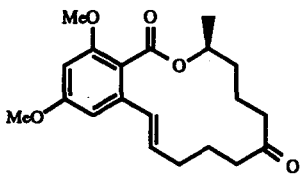

(11)




(12)




(13)




(14)

Controlled reaction between (12) and N-bromosuccinimide in the presence of ultraviolet light, produced exclusively the E-cinnamyl bromide (13) in a satisfying 62% yield.[10] Finally, treatment of the bromide (13) with tris(trimethylsilyl)silane ($C_6H_5Me$, AIBN, 80°C, syringe pump over 8h)[11] resulted in clean 14-endo-trig macrocyclisation producing the known dimethyl ether (14) of (-)-zearalenone in 55% yield. Deprotection of the dimethyl ether (14)[3f] then gave (-)-zearalenone (1), white crystals, m.p. 164-5°C ($Et_2O$-hexane), $[\alpha]_D$ -191° (c. 0.5, $CHCl_3$) which was identical in all respects (m.p. and mixed, optical rotation, chromatography, i.r., n.m.r.) with naturally derived material.

**Acknowledgements**

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