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ASYMMETRIC 1,4-ADDITIONS TO γ -MENTHYLOXYBUTENOLIDES. (part II)¹
 ENANTIOSELECTIVE SYNTHESIS OF LIGNAN TYPE COMPOUNDS.

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Abstract: Addition of dithianes, derived from alkyl- and aryl-aldehydes, to (5R)-menthyloxy-2[5H]-furanone followed by quenching with substituted benzylhalides or a benzaldehyde gives enantiomerically pure lignan type compounds in good yields.

Currently an increasing activity in the stereocontrolled synthesis of lignans is observed² due to the interesting biological activity³ that is associated with many members of this class of compounds. Chiral butenolides can serve as excellent starting materials for these syntheses as they have served in the preparation of many chiral building blocks with arrays of methyl- and hydroxy-substituents at vicinal or remote stereogenic centers⁴. In particular tandem conjugate additions-alkylations to non-chiral and chiral butenolides have been reported to provide usefull routes to several lignans⁵. We have extensively explored menthyloxyfuranone **1** as a chiral synthon due to the excellent stereocontrol exerted by the γ -menthyloxy substituent, the easy way of preparation and the use of cheap d- or l- menthol as chiral auxiliary⁶. A very recent report of Pelter, Ward and coworkers⁷ on the asymmetric synthesis of a dibenzylbutyrolactone lignan precursor prompts us to report our results in the formation of lignan type compounds.

Table: products and yields of 1,4-addition/alkylation and desulphurisation

entry	R ₁	R ₂	R ₃	yield of 4 (%)
a	CH ₃	CH ₃	PhCH ₂	65
b	CH ₃	(CH ₃ O) ₂ C ₆ H ₃	PhCH ₂	76
c	CH ₃	(CH ₃ O) ₂ C ₆ H ₃	(CH ₃ O) ₂ C ₆ H ₃ CH ₂	85
d	Menth	CH ₃	H	71
e	Menth	CH ₃	CH ₃	72
f	Menth	Ph	H	71
g	Menth	Ph	CH ₃	69
h	Menth	(CH ₃ O) ₂ C ₆ H ₃	(CH ₃ O) ₂ C ₆ H ₃ CH ₂	81

The addition of the dithianes **2**, prepared from several alkyl and aryl aldehydes, to enantiomerically pure butenolide **1** proceeds smoothly if the dithiane is a bis(phenylthio)acetal⁸ (entry 4,6; enolate quenched with NH₄Cl aq.) and is a poor reaction if the dithiane is a 1,3-dithiane⁹ (scheme). Quenching of the resulting lactone enolate anion with a benzylbromide (entry 1-3,8) or methyl iodide (entry 5,7) resulted in single diastereoisomers, (NMR,TLC) with the all trans geometry at the lactone ring¹⁰. The trans stereochemical assignment is based on ¹H-NMR and by analogy with previous results^{1,6}; for example $J_{H3,H4} = 3.3\text{Hz}$ and $J_{H4,H5} = <0.2\text{Hz}$ in compound **3e** support the C3-C4 and C4-C5 trans configurations. Desulphurisation with Raney-Nickel is a nearly quantitative process which results in the dibenzylsubstituted butyrolactones in enantiomerically pure form in 60-81% yield. Similar addition of the lithio derivative of 3-benzyloxy-4-methoxybenzaldehyde bis(phenylthio)acetal to **1** followed by quenching with 3-benzyloxy-4-methoxybenzaldehyde provides **5** as a single diastereoisomer in 50% yield. The configuration at the exocyclic stereogenic center as depicted (scheme) was assigned on the basis of extensive COSY and NOESY experiments.

In conclusion we describe a short and efficient asymmetric synthesis of chiral lignan type compounds. Application of this strategy in the synthesis of Pinoresinol and related lignans is currently under investigation.

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10. Based on the coupling constants in the 300 MHz ¹H-NMR spectra; all compounds showed spectral and analytical data in accordance with the proposed structures.