Tetrahedron: Asymmetry Vol. 1, No. 12, pp. 857-860, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

ASYMMETRIC SYNTHESIS OF HOMOCHIRAL DIBENZYLBUTYROLACTONE LIGNANS BY CONJUGATE ADDITION TO A CHIRAL BUTENOLIDE

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(*Received* 6 *November* 1990)

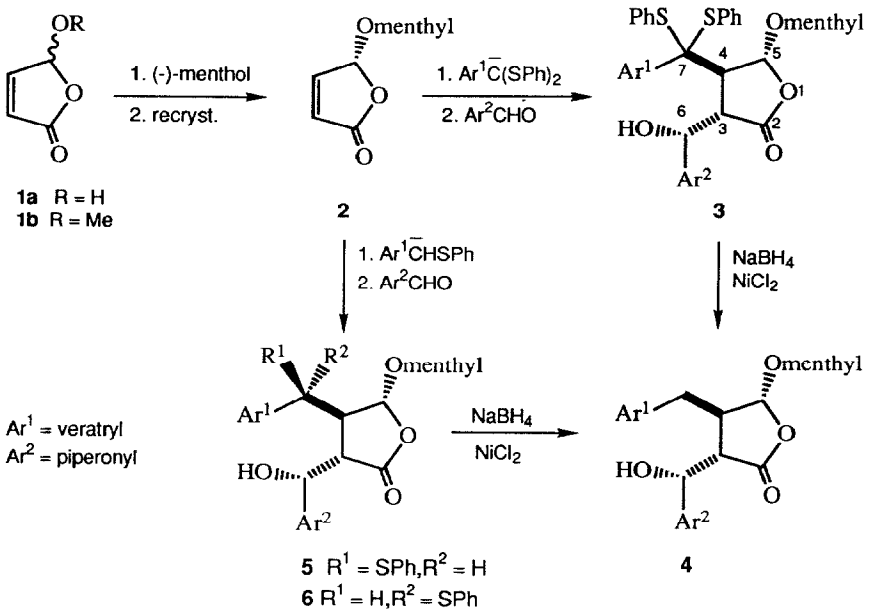
Abstract: Addition of sulphur stabilised carbanions to a chiral non-racemic butenolide followed by reaction with an aromatic aldehyde affords a short synthesis of homochiral dibenzylbutyrolactone derivatives. Desulphurisation of the first formed adducts proceeds in almost quantitative yield to afford the parent lignan.

Lignans display a wide range of biological activity.[1,2] For example, podophyllotoxin and its demethyl derivative show powerful and specific cytotoxic activity,[3,4] and derivatives of these compounds are used clinically against small cell lung cancer and testicular cancer.[5,6] Also of interest is the alkoxy substituted lactone justicidin P which is structurally related to the aryltetralin series and which displays significant anti-viral activity.[7]

We have previously shown that tandem conjugate addition reactions to butenolide provide an efficient route for the synthesis of dibenzylbutyrolactone derivatives which can be cyclised to afford arylnaphthalene and aryltetralin lactones including analogues of podophyllotoxin.[8,9] We have now shown that homochiral dibenzylbutyrolactone derivatives can be synthesised in this way by utilising the chiral non-racemic butenolide (**2**),[10] which bears an extra alkoxy group as compared with butenolide, our previous substrate.

The butenolide (**2**) has been previously prepared by equilibration of a mixture of diastereoisomers by reacting 4-hydroxybutenolide (**1a**), obtained by singlet oxygen addition to furoic acid, with (-)-menthol.[10] We have found that (**2**) can also be prepared from 4-methoxybutenolide (**1b**), which is commercially available.[11] The required diastereoisomer (**2**) can be obtained by crystallisation from pentane and the yield enhanced by epimerisation of the other diastereoisomer under acidic conditions.[10] ***Thus, enantiomerically pure synthon (2) is now cheaply and readily available.***

Treatment of (**2**) with the lithio derivative of 3,4-dimethoxybenzaldehyde bis(phenylthio)acetal[9] followed by reaction with piperonal gave a ***single*** adduct (**3**) in 83% yield. The all ***trans*** arrangement



around the butyrolactone ring was assigned by analogy with earlier results[8,9,12] and was supported by spectroscopic and chemical correlation with the thioether adducts described below. The ***threo*** configuration of the benzylic OH group was assigned on the basis of the observed coupling constant (8.5Hz)[13,14] between H-3 and H-6 and was consistent with the involvement of the enolate in a chelate-controlled six-membered cyclic transition state (see Figure 1).[15,16] Treatment of (**3**) with nickel boride[1] gave the desulphurised product (**4**) in quantitative yield. The C4-C5 ***trans*** configuration in (**4**) was supported by the small coupling constant (2.2Hz) between H-4 and H-5. There was no sign, by ^{13}C or ^{1}H n.m.r, of the presence of diastereoisomers. The asymmetry of menthol has thus been transferred first to C-5 and then, specifically and in one step to C-4, C-3 and C-6 of (**3**) and (**4**).

Treatment of (**2**) with the lithio derivative of 3,4-dimethoxybenzyl phenyl sulphide[8] followed by reaction with piperonal gave a 1:1 mixture of two diastereoisomeric products (**5**) and (**6**) in a 74% overall yield. The two isomers could be separated by reverse phase preparative h.p.l.c. and gave n.m.r. spectra which suggested that they differed only in the configuration of the SPh group. Thus the main differences between the spectra were the chemical shifts of H-5 (5.45 in (**5**), 6.12 in (**6**)) and H-3 (3.03 in (**5**), 2.60 in (**6**)). The high value of the coupling constant between H-4 and H-7 suggests that they are ***anti*** to one another in both isomers. The chemical shift differences could then be rationalised by postulating that H-3 in (**5**) and H-5 in (**6**) would be de-shielded by the neighbouring SPh group. The spectral assignments of (**5**) and (6) were fully supported by COSY measurements.

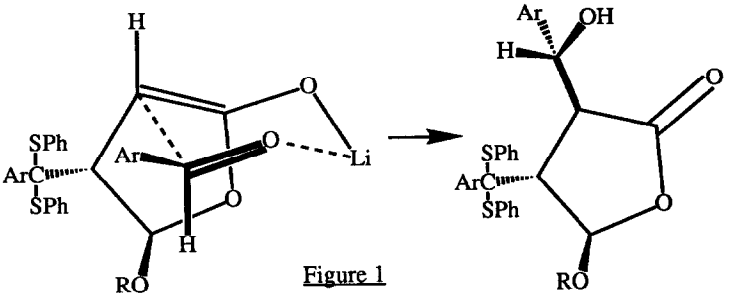


Figure 1

The conclusion that (**5**) and (**6**) differ only in their configuration at C-7 was confirmed by the observation that on treatment with nickel boride both compounds were converted in almost quantitative yield into a single dibenzylbutyrolactone derivative which was readily identified as (**4**), identical with the product from (**3**). ***Thus all compounds (3), (5) and (6) have the same absolute configurations at C-6, C-3 and C-4.*** The complete structure and configuration assigned to these compounds was confirmed by carrying out an X-ray analysis on (**6**) (see Figure 2).[18] These reactions therefore provide a short asymmetric synthesis of dibenzylbutyrolactone lignans which also represent valuable precursors for the synthesis of optically active aryltetralin lignans and justicidin P derivatives. Further elaboration of these compounds will be described in a later publication.

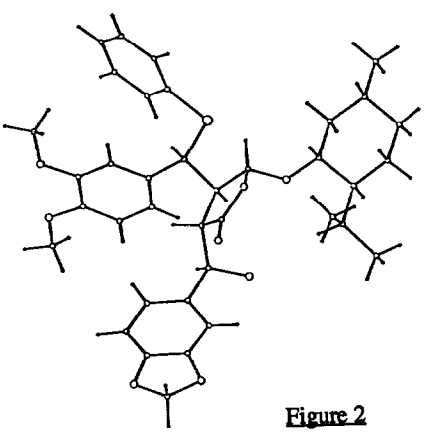


Figure 2

Acknowledgement.

We are grateful to the Wellcome Foundation for providing financial support for the project and for running high field and COSY spectra. We thank Professor M. B. Hursthouse and Dr. D. Ando (Queen Mary College, London) for carrying out the X-ray analysis.

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18. Details of the X-ray determination may be obtained from Prof. M. B. Hursthouse, Queen Mary College, London.