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Asymmetric Syntheses of Lignans of the Dibenzylbutyrolactone, Dibenzylbutanediol, Aryltetralin and Dibenzocyclooctadiene Series

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Abstract. General procedures are outlined for the asymmetric syntheses of lignans of the dibenzylbutyrolactone, dibenzylbutanediol, aryltetralin and dibenzocyclooctadiene series, from tandem addition products derived from 4-menthyloxybutenolide.

The wide ranging biological activities of lignans makes them prime synthetic targets.[1,2,3] In particular, the use of podophyllotoxin and its derivatives as anti-cancer and antiviral agents,[4,5,6,7] has aroused much scientific and commercial interest. Justicidin P is also a potent antiviral agent[8], and lignans of the dibenzocyclooctadiene series display strong anticancer properties.[9] The cytotoxic dibenzylbutyrolactone mammalian metabolite, enterolactone, is thought to be involved in problems of cell division during pregnancy, and has anti-tumour activity.[10]

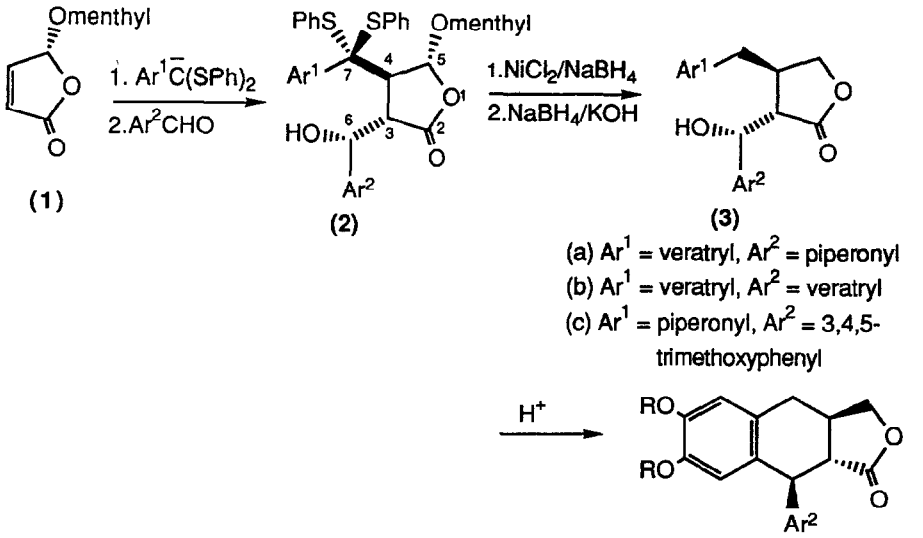
We recently disclosed[11] that the chiral synthon (1) is readily produced from commercially available 4-methoxybutenolide and that it takes part in high yield tandem addition reactions to give homochiral compounds (2), in which the chirality of the menthyloxy group has been transmitted to four new chiral centres. Compounds (2) contain all the carbon atoms of lignans with good functionality. Since our paper, Feringa has used precisely this approach to synthesise (-)-eudesmin, a furofuranoid lignan, [12] whilst (-)-epipodophyllotoxin and (-)-podophyllotoxin have also been made by a lengthy series of reactions starting from (1).[13]

We here report the asymmetric syntheses of four classes of lignans. using intermediates made by tandem addition reactions involving butenolide (1).

1-Aryltetralin lignans

Compounds (2) are readily and efficiently desulphurised by nickel boride.[11] Removal of the menthyloxy group then yields (3) in overall yields[#] of 40 - 60%.[13] Cyclisation of (3a-c)[14] then gives (4a-c) in nearly quantitative yields (Scheme 1).

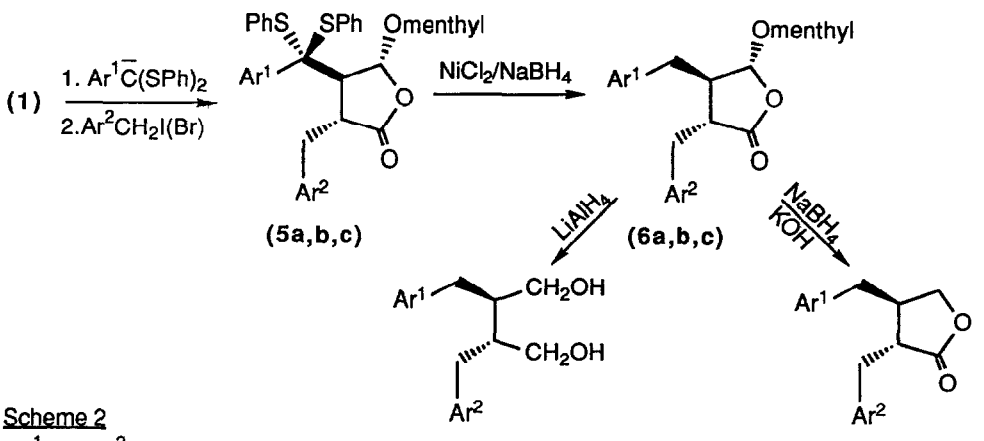
[#]All yields are of isolated, fully characterised products.



Scheme 1

Compound (4c) is (-)-4-deoxyisopodophyllotoxin[14] and (3c) is the 6-hydroxydibenzylbutyrolactone lignan, (-)-6-epi-podorhizol.[15]

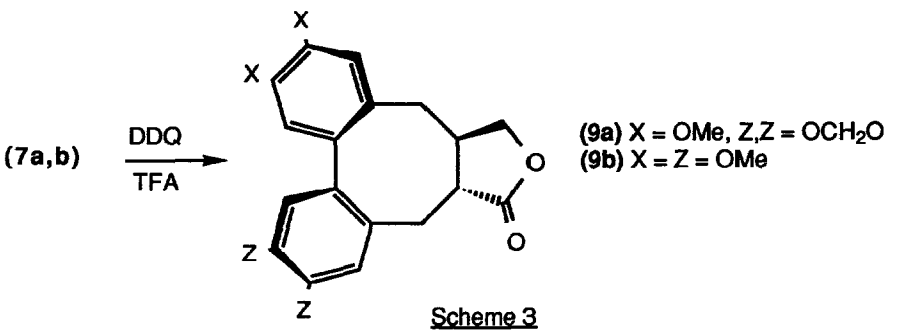
Dibenzylbutyrolactones. We have now carried out chiral tandem additions to (1) using benzyl iodides or bromides to trap the intermediate carbanions to yield homochiral adducts (5) (80 - 100%) (Scheme 2).



Scheme 2
(Ar^1 and Ar^2 as for Scheme 1)

The desulphurisation of (5) proceeded in an essentially quantitative yield to give the interesting lignan derivatives (6). The reduction of (6) has to be carried out with care, as if the base is added prior to the borohydride then epimerisation occurs at C-4. The reaction is best carried out by adding sodium borohydride followed by potassium hydroxide when (7) results in 60-65% yield. These reactions constitute syntheses of (-)-kusunokinin[16] (**7a**), (-)-di-O-methylmatairesinol[17] (**7b**) and (-)-yatein[18] (**7c**). Reduction of (6) using lithium aluminium hydride gave the corresponding dibenzylbutanediols (8), including (-)-dimethyl-secoisolariciresinol (**8b**)[19] and (-)-dihydroclusin (**8c**).[20]

Dibenzocyclooctadienes. We have recently shown that the action of DDQ in trifluoroacetic acid on 3,4-dibenzyl-tetrahydrofurans related to (7) leads to (+)-dibenzocyclooctadienes, the optical rotation being governed by the configuration of the biphenyl unit.[14] We have now successfully extended this process to the lactones (7) and find that compounds (+)-(9) are produced in yields (35-55%), consistent with our previous findings, and belonging to the same stereochemical series (Scheme 3).



Scheme 3

The configuration of (9) was established by n.m.r. techniques[21,22] and by the optical rotation.[3,23] The process constitutes a synthesis of (+)-5-detigloyloxy-steganolide C[24] (**9b**).

Thus tandem addition products from (1) can lead to four different classes of enantiomerically pure lignans. Further experiments using other adducts related to (2) and (5) are in hand.

Acknowledgement.

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