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A SHORT EFFICIENT SYNTHESIS OF TRANS-DIBENZYLBUTYROLACTONES EXEMPLIFIED BY THE SYNTHESIS OF DI-O-METHYL COMPOUND X (HPMF) AND AN ANTI-TUMOUR EXTRACTIVE.

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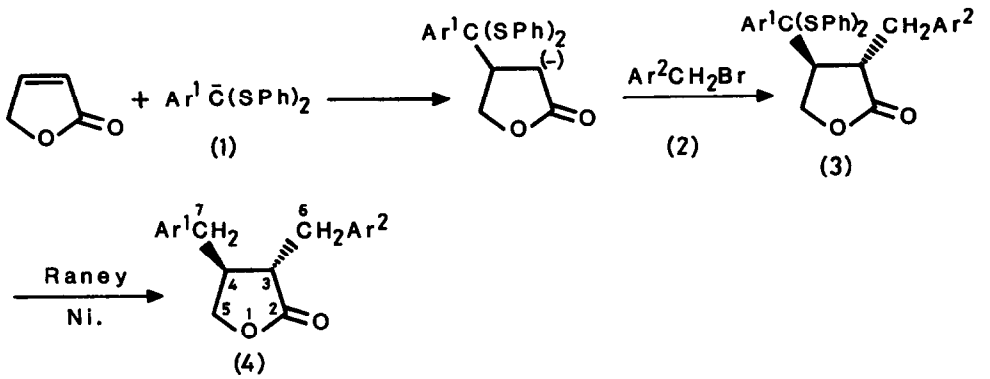
An efficient synthesis of trans-dibenzylbutyrolactones, applicable to very many of those lignans, is outlined. Two examples including di-O-methyl compound X (HPMF) are given.

That lignans may exhibit varied physiological activities has been long known[1,2] and great interest has been shown in their anti-tumour properties.[3] Very recent and striking observations describe the cyclic excretion in the female, particularly during the luteal phase of the menstrual cycle and early pregnancy, of a lignan, compound X (HPMF) (4c, Ar^1 = Ar^2 = 3-hydroxyphenyl)[4], and a related diol. The biological significance of these compounds remains to be established but their resemblance to anti-tumour lignans suggest a relationship to the control of cell growth. Already two syntheses of HPMF have been reported.[5,6] Both are multistep and one[5] proceeds in 35% yield from a fairly advanced precursor whilst no yields are given in the other case.[6]

As an offshoot from a broad attack on lignan synthesis[7,8] we now report a short efficient synthesis of trans-dibenzylbutyrolactones applicable whether the aryl groups are the same or different, both being derived from arylaldehydes by standard high yield steps.



We utilise a tandem conjugate addition[9] involving Michael addition of the anions of aryldiphenylthiomethanes (1) to butenolide at -78°, followed by trapping the anionic intermediate with a benzyl bromide (2) (Scheme) to give compounds (3) in ca 65-70% isolated yield of pure product. The phenylthioacetals were chosen for several reasons, particularly the ready displacement of the phenylthio group by heavy metals, which will be discussed separately. In the present case treatment of (3) with Raney nickel in refluxing ethanol gave the required compounds (4) in quantitative yields, thus making these compounds readily available.

We have carried through this process to give (3a) (Ar^1 = Ar^2 = 3-methoxyphenyl) and hence (4a), di-O-methyl HPMF in an overall yield of 68%. As (4a) has previously been converted to HPMF in 80% yield[5] this constitutes a formal total synthesis of HPMF. (There is no reason why the process should not be carried out with 3-benzyloxyphenyl groups if hydrogenation is preferred as a final step).

When the scheme is carried out with (1b) (Ar^1 = 3,4-methylenedioxyphenyl) and (2b) (Ar^2 = 3,4-dimethoxyphenyl) then the final product (4b) is produced in 67% yield overall. This compound is a natural product isolated from an extract of Bursera schlechtendalii[10] which exhibited anti-tumour activity.

Compound (3a) had ν_{max} 1780cm^{-1}; λ_{max} 260sh.(3.81) and 275(3.85)nm; m/e 433 (M-SPh); δ($CDCl_3$) 4.41dd (J=3,10, H-5a), 3.55dd (J=8,10, H-5b), 2.97m(H-4), 3.35m(H-3), 3.11dd (J=4,13, H-6a), 2.80dd (J=6,13, H-6b), 6.4 - 7.4m(arom.), 3.69s and 3.70s(OMe).

Compound (4a) had ν_{max} 1780cm^{-1}; λ_{max} 275(3.49) and 282(3.47)nm; M^+ 326.1518 ($C_{20}H_{22}O_4$); δ($CDCl_3$)4.08m(H-5a), 3.82m(H-5b), 2.96m(H-3), 2.54m(H-4, H-6, H-7), 6.5 - 7.3m(arom.) 3.72s and 3.74s(OMe).

Compound (3b) had ν_{max} 1775cm^{-1}; λ_{max} 257(2.68) and 285(3.41)nm; m/e 477(M-SPh); δ($CDCl_3$) 4.43dd (J=3,10, H-5a), 3.54dd (J=8,10, H-5b), 2.93m(H-4), 3.24m(H-3), 3.08dd (J=4, 13, H-6a), 2.77dd (J=5,13, H-6b), 6.4 - 6.7m and 7.26m(arom.) 3.74s and 3.84s(OMe), 5.94s (OCH_2O).

Compound (4b) had ν_{max} 1775cm^{-1}; λ_{max} 246(3.66) and 285(3.73)nm; M^+ 370.1418 ($C_{21}H_{22}O_6$); δ($CDCl_3$) 4.1m(H-5a), 3.8m(H-5b), 2.90m(H-3), 2.52m(H-4, H-6, H-7), 6.46m and 6.69m(arom.) 3.82s and 3.84s(OMe), 5.90s(OCH_2O).

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