Synthesis and Stereochemistry of Dilactones Related to Strigol

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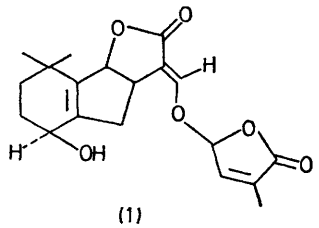
Summary A general approach to the synthesis of strigol (**1**) analogues has been developed which involves the stereospecific coupling of bromobutenolides (**3a**) and (**3b**) with the sodium enolate (**2**) of 3-(hydroxymethylene)-dihydrofuran-2(3*H*)-one to give dilactones (**4a**) and (**4b**) one of which showed significant cytotoxicity against Hela cells in preliminary testing to evaluate the potential anticancer activity of strigol analogues.

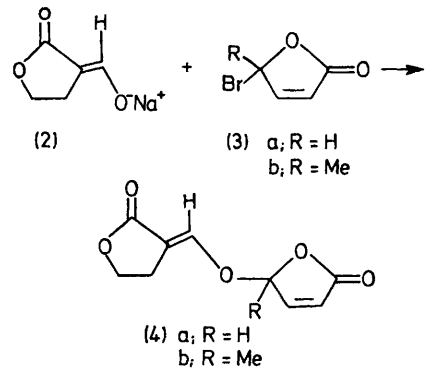
STRIGOL (**1**), a potent seed germination stimulant, was recently isolated from the root exudates of the cotton plant.[1,2] As part of a programme to evaluate the anticancer activity of a variety of unsaturated lactones, we



(1)

have investigated the synthesis of the alkoxy-dilactone portion of the strigol (**1**) molecule as a first step in determining the potential antitumor activity of strigol analogues. The cytotoxic and antitumor activity of a large number of natural α-methylene-γ-lactones has been established[3,4] and since the physiological activity of β-alkoxy-α-methylene lactones remains largely unexplored, a general approach to the synthesis of such compounds may be of considerable interest.

The synthesis of two representative dilactones (**4a**) and (**4b**), has been accomplished by a coupling step which appears to produce the *E* isomer specifically.



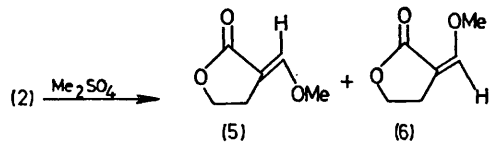
(2) (3) a; R = H b; R = Me

(4) a; R = H b; R = Me

SCHEME 1

The enolate salt (**2**) was prepared in 95% yield from γ-butyrolactone.[5,6] Reaction of (**2**) with bromobutenolide (**3a**)[7] at room temperature in acetonitrile for 24 hours gave (**4a**) (Scheme 1),† m.p. 117—118° (toluene), λ_{max} 230 nm (ε 12,000), ν_{max} (KBr) 1776, 1730, and 1675 cm^{-1}, *m/e* 196 (M^+) and 83 (corresponds to the butenolide fragment $C_4H_3O_2$). The n.m.r. spectrum of (**4a**) further supported the assigned structure with signals for the methylene vinyl proton and the β-butenolide proton appearing as a complex multiplet centred at δ 7·3. The signals at δ 4·35 (2H, t, *J* 7·5) and 2·92 (2H, m) were assigned to the furan-2(3*H*)-one ring methylene protons. Signals at δ 6·40 (1H, d, *J* 6)-2(3*H*)-

and 6·38 (1H, brs) were assigned respectively to the α and γ-hydrogens on the butenolide ring.



SCHEME 2

In a similar fashion reaction of (**2**) with bromobutenolide (**3b**)[8] gave (**4b**) as a homogeneous syrup,† λ_{max} 230 nm (ε 14,000), ν_{max} ($HCCl_3$) at 1776, 1751, and 1680 cm^{-1}, *m/e* 210 (weak, M^+) and 97 (strong, corresponds to the methylbutenolide fragment $C_5H_5O_2$). The n.m.r. spectrum of (**4b**) showed a signal at δ 1·83 (3H,s) and lacked the γ-butenolide hydrogen which appeared at δ 6·38 in (**4a**). The spectrum was otherwise very similar to that of (**4a**) showing a complex multiplet at δ 7·3 (2H) and signals at δ 6·37 (1H, d, *J* 5·5), 4·38 (2H, t, *J* 7·5), and 2·92 (2H, m, *J* 2·5, 7·5).

Assignment to the *E* isomer was made on the basis of the observed absorption for the α-methylene vinyl proton which appeared as part of a multiplet centred at δ 7·3 in both compounds. The analogous highly deshielded proton in strigol appears at about δ 7·4. Further evidence for this assignment was obtained by analysis of the n.m.r. spectrum of the 6:1 mixture of (*E*)- and (*Z*)-3-(methoxymethylene)-dihydrofuran-2(3*H*)-ones [(**5**) and (**6**)][9] produced by reaction of (**2**) with dimethylsulphate in acetone (Scheme 2). The vinyl proton signals in this mixture appeared at δ 7·1 in (**5**) and 6·55 in (**6**). The fact that the coupling reaction produces the *E* isomer would suggest that this approach could be extended to construction of this portion of the strigol molecule although substitution on the furanone enolate would be expected to influence the isomer distribution.‡

In preliminary testing, compound (**4b**) has shown significant cytotoxic activity against Hela cells (ED50 < 5 μg/ml). Compounds (**4a**) and (**4b**) and related compounds which will be synthesized by this general approach will undergo further testing to evaluate their potential cytotoxic, antitumor, and seed germination stimulating activity.

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† Compounds (**4a**) and (**4b**) gave satisfactory elemental analyses.

‡ *Note added in proof:* Strigol has recently been synthesized; J. B. Heather, R. S. D. Mittal, and C. J. Sik, *J. Amer. Chem. Soc.*, 1974, **96**, 1976.

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