

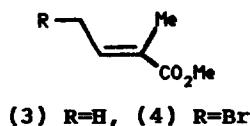
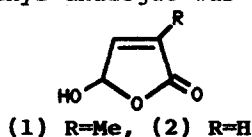
**2,5-DIMETHOXY-2,5-DIHYDROFURAN: A CONVENIENT SYNTHON FOR A NOVEL
MONO-PROTECTED GLYOXAL; SYNTHESIS OF 4-HYDROXYBUTENOLIDES**

Stephen C.M. Fell* and John B. Harbridge

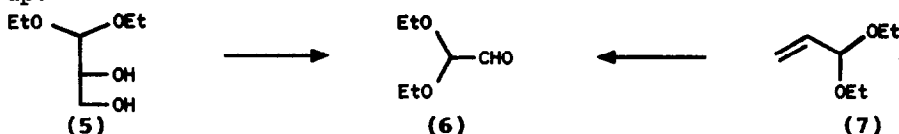
Beecham Pharmaceuticals Research Division, Brockham Park,
Betchworth, Surrey, RH3 7AJ, England.

Abstract: Ozonolysis, followed by a reductive work up of 2,5-dimethoxy-2,5-dihydrofuran generates the symmetrical bis-aldehyde (9) which reacts *in situ* with certain stabilized phosphoranes. Hydrolysis of the resultant alkene acetals affords 4-hydroxybutenolides (1) and (2).

Recently we required a simple, high yielding route to the 4-hydroxybutenolide (1). A previously reported¹ synthesis from methyl tiglate (3), via oxidation of the allylic bromide (4), gave a poor overall yield of (1), (the 4-methyl analogue was readily available *via* a Wittig condensation).

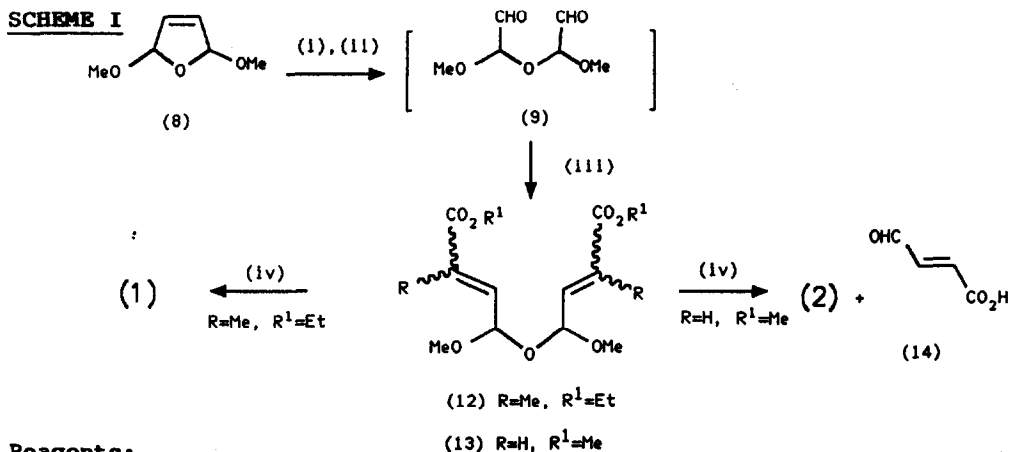


Traditionally, diethoxy acetaldehyde (6) has been used as a versatile mono-protected glyoxal. This has been prepared by oxidative cleavage of glyceraldehyde diethyl acetal (5) using lead tetraacetate,² and by ozonolysis of acrolein diethyl acetal (7) followed by triphenylphosphine work up.³



Both of these routes suffer from the disadvantage of the need to isolate the acetal (6) from the formaldehyde generated during the process.

We wish to report that 2,5-dimethoxy-2,5-dihydrofuran (8), a cheap commercially available reagent⁴ readily undergoes ozonolysis to the bis-aldehyde (9) *via* reduction of the ozonide with triphenylphosphine, Scheme I. The aldehyde (9) thus generated need not be isolated but can be trapped, *in situ* with the stabilized phosphoranes (10) and (11) to give the alkene acetals (12) and (13) respectively.

**Reagents:**

(i) O₃, CH₂Cl₂, -78°C; (ii) Ph₃P RT; (iii) Ph₃P=CR.CO₂R¹, (10) R=Me, R¹=Et, (11) R=H, R¹=Me; (iv) 1:1, 5M HCl, dioxan, 100°C, 2h.

Triphenylphosphine oxide is the only side product in both steps and can be readily separated by extraction of the product into hexane.

2,5-Dimethoxy-2,5-dihydrofuran (8) is supplied as approximately a 2:1 mixture of diastereoisomers. Evidence from the ¹H.n.m.r. spectrum of (12),⁵ suggests this isomeric ratio is reflected in the product (12), and the simplicity of the spectrum also demonstrates that only one geometrical isomer is formed during the Wittig condensation. This selectivity was not observed for example (13)⁶, where the ¹H.n.m.r. data suggests a mixture of E and Z isomers. The crude acetal (12), [which may be purified by 'flash' chromatography on silica gel], is readily hydrolysed with dilute hydrochloric acid to give the 4-hydroxybutenolide (1), in 60% yield from the furan (8). Similarly, hydrolysis of the E and Z isomers of (13) affords an inseparable mixture of (2) and fumaraldehydic acid (14) in a total yield of 74% from (8).

Acknowledgement: The authors are indebted to Dr. G. Burton for helpful discussions throughout this work.

References and Notes

- G. Pattenden and B.C.L. Weedon, *J.Chem.Soc.(C)*, (1968), 1984.
- A.R. Battersby, J. Staunton, H.R. Wiltshire, B.J. Bircher and C. Fuganti, *J.Chem.Soc., Perkin Trans. 1*, (1975), 1162.
- H.J. Bestmann and P. Ermann, *Chem.Ber.*, (1983), 116, 3264.
- Obtained from Aldrich Chemical Company and used without purification.
- ¹H.n.m.r., 90MHz spectrum of diastereoisomers of (12): δ(CDCl₃) 1.29 (3H, t, J 7Hz) 1.93 (3H, d, J 2Hz), 3.30 (minor) and 3.35 (major) (3H, s), 4.19⁻(2H, q, J 7Hz), 5.36⁻(major) and 5.50 (minor) (1H, d, J 7Hz, 6.64 (1H, dq, J 2⁻, 7Hz).
- The ¹H.n.m.r. spectrum (250MHz) of (13) showed a complex mixture of at least five isomers.

(Received in UK 31 May 1990)