Tetrahedron Letters, Vol. 22, No. 15, pp 1467 - 1470, 1981
Printed in Great Britain

0040-4039/81/151467-04$02.00/0

NEW SYNTHETIC ENTRIES TO γ-HETEROMETHYL-SUBSTITUTED α,β-BUTENOLIDES

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Summary: The title compounds have been obtained from C_3 plus C_2 synthons by a variety of chemical and photochemical methods.

Butenolide precursors have been recently used in the synthesis of antileukaemic lignans[1,2] and prostaglandin analogs[3]. Furthermore, very recently the antibiotic γ-chloromethyl-γ-hydroxy-α-methyl-α,β-butenolide (lepiochlorin) has also been synthesized[4]. This prompts us to publish our own results in the field of butenolide synthesis.

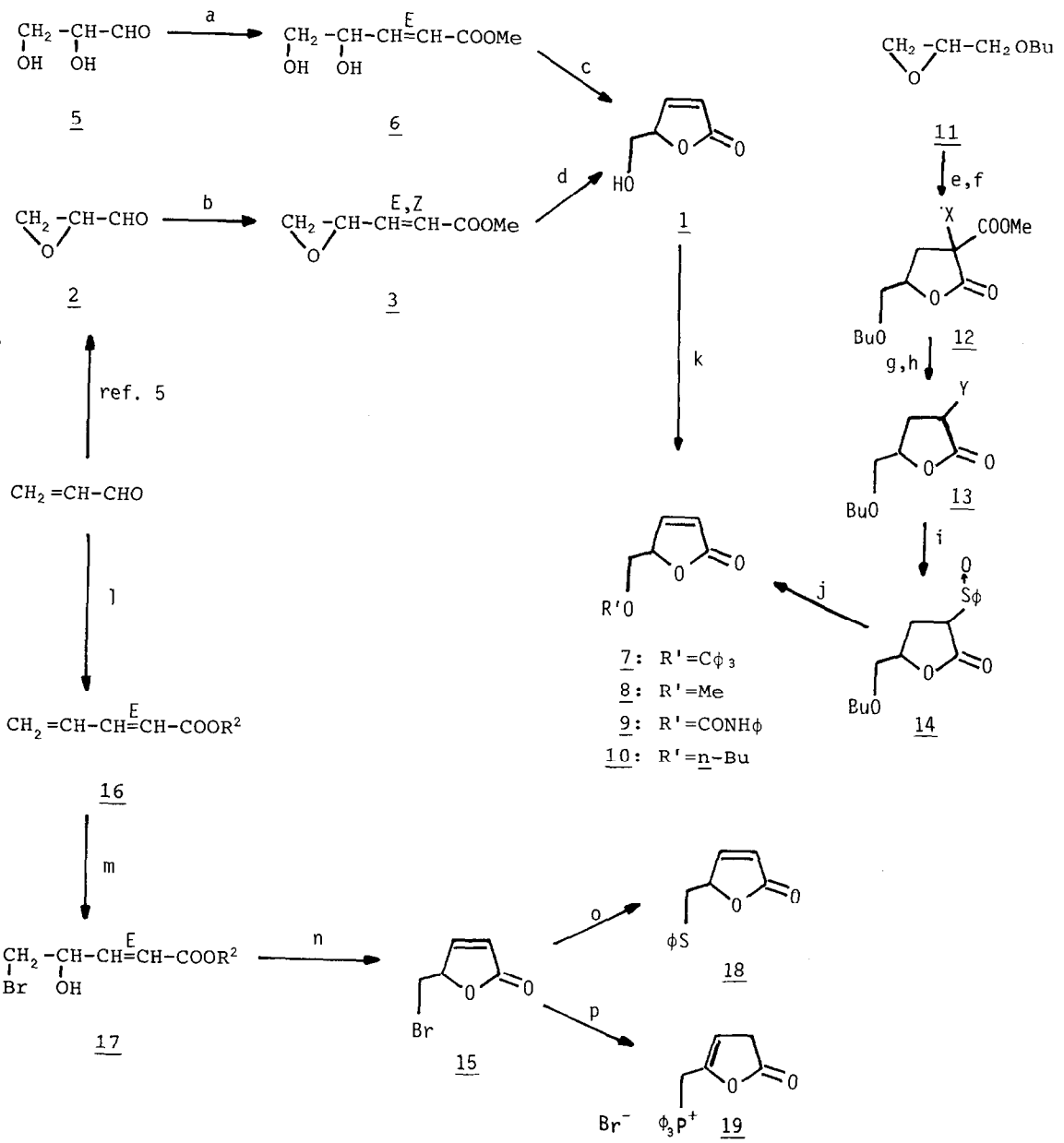
Our first target, γ-hydroxymethyl-α,β-butenolide 1 could be obtained by two methods as shown in the Scheme. Epoxidation[5] of acrolein (H_2O_2, pH 8) gave glycidaldehyde 2 in high conversion, which without isolation was subjected to Wittig reaction, yielding in 23% overall yield from acrolein a 2:3 E:Z mixture of epoxyesters 3. Acidic treatment of the Z isomer (separated by t.l.c.) or, more conveniently, of the mixture of E:Z isomers, led to 1 (10% overall yield from acrolein). The main byproduct 4, which comes from (E)-3, was easily separated by distillation. Alternatively, 1 could also be obtained from glyceraldehyde 5 by Wittig reaction to diolester[6] 6 (80%) followed by UV irradiation with a 400 W medium-pressure mercury lamp; the overall yield of 1 from 5 was 75%. Derivatives 7 (9%, m.p. 163-4°C), 8 (41%) and 9 (34%, m.p. 114-6°C) were prepared from 1 as shown in the Scheme.

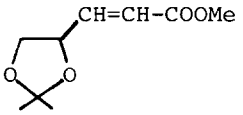
Another approach to γ-alkoxymethyl-α,β-butenolides is exemplified in the Scheme for the case of n-butyl ether 10. Condensation of n-butoxymethyloxirane 11 with sodium dimethyl malonate gave the lactone 12 (X=H) (53% yield), which upon chlorination[7] yielded 12 (X=Cl). One-pot acidic treatment of the last led to the chlorolactone 13 (Y=Cl). Replacement of chlorine led to 13 (Y=PhS), whose oxidation yielded 14 which without further purification was heated to afford 10 in 39% overall yield from 11.

Our second target, γ-bromomethyl-α,β-butenolide 15, could also be prepared from acrolein in two ways, both involving photochemical mediated lactonization of appropriate precursors. Thus, the easily polymerizable butadiene derivatives

16 were prepared by Wittig (R^2=Me, 25% yield) or Knoevenagel[8] (R^2=H, 70% yield) reactions.

Scheme





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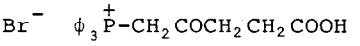

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a: ϕ_3P=CHCOOMe / ref. in C_6H_6; b: ϕ_3P=CHCOOMe / H_2O-MeOH / r.t.; c: UV hν, 400 W/ MeOH, H^+ / r.t.; d: $HClO_4$ / ref. in acetone; e: $(MeOCO)_2CHNa$ / ref. in MeOH; f: SO_2Cl_2 / 80°C; g: ref. in HCl-AcOH; h: NaSPh / ref. in EtOH; i: $NaIO_4$ / MeOH-H_2O / r.t.; j: ref. in toluene; k (R'=Me): CH_2N_2 / BF_3-ether; k (R'=Cϕ_3): ϕ_3CCl / pyr.; k (R'=CONHPh): PhNCO / ref. in C_6H_6; l (R^2=H): $H_2C(COOH)_2$ / pyr. / 70°C; l (R^2=Me): ϕ_3P=CHCOOMe / H_2CCl_2 / r.t.; m (R^2=H): Br_2 / $NaHCO_3$ / H_2O / r.t. or NBS / H_2O / r.t.; m (R^2=Me): NBS / H_2O / r.t.; n (R^2=H): UV hν, 400 W / H_2O, H^+ / r.t.; n (R^2=Me): UV hν, 400 W / MeOH, H^+ / r.t.; o: NaSPh / DME / 0°C; p: ϕ_3P / C_6H_6 / r.t.

Bromohydrins 17 could be obtained in 50-65% yield from compounds 16 by treatment with either aqueous NBS or bromine[9] as shown in the Scheme. Irradiation of 17 with the above mentioned lamp under acidic conditions led to 15 in 56-75% yield. The best way to 15 (24% overall yield from acrolein) was via 16 (R^2=H) and its reaction with bromine in aqueous $NaHCO_3$.

The useful intermediate 15 was converted into γ-phenylthiomethyl-α,β-butenolide 18 by treatment with 1 equiv. of sodium phenylthiolate (25%). Unexpectedly, however, reaction of 15 with triphenylphosphine afforded the unstable (2-oxo-2,3-dihydro-5-furylmethyl)triphenylphosphonium bromide 19 (65%; m.p. 172-8°C), rather than the expected unrearranged salt. On standing 19 hydrolyzes to (4-carboxy-2-oxobutyl)triphenylphosphonium bromide 20 (m.p. 231-3°C).

We are presently exploring the preparation of more ether derivatives of 1 and other hetero derivatives from 15. Also in the following paper[10], an entry to ethers of chiral 1 is described.

All compounds mentioned showed the expected spectroscopic behaviour and the new ones exhibited satisfactory elemental analyses.

ACKNOWLEDGEMENTS

We thank Dr. P. de March and Dr. A. Virgili for running the mass spectra, and AICAR S.A. (Cerdanyola) for a generous gift of compound 11. Grants (to C.E. and S.V.) from the former Ministerio de Educación y Ciencia (Spain) and financial support from Comisión Asesora de Investigación Científica y Técnica are gratefully acknowledged.

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(Received in UK 26 January 1981)