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A PHOSPHORANE MEDIATED SYNTHESIS OF TETRONIC, THIOTETRONIC AND TETRAMIC LACTONES

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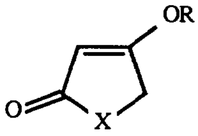
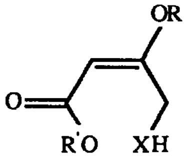
Summary : Intramolecular reaction of stabilised γ-acylphosphonium ylides derived from esters, thiolesters and amides with γ-lactone carbonyl groups resulted in the formation, by a Wittig-type cyclisation, of tetronic, thiotetronic and tetramic γ-lactones respectively.

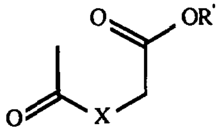
Many natural products from diverse origins possess the tetronate (**1a**),[1] thiotetronate (**1b**)[2] or tetramate (**1c**)[3] nuclei as key structural elements.



(**1a**) X = O
(**1b**) X = S
(**1c**) X = NH



(**2**)



(**3**)

In the preparation of the ring systems (**1**) substituted derivatives of (**2**) or (**3**) are often used as starting materials, although these may present synthetic problems in themselves or can require the use of strong bases or vigorous conditions to effect cyclisation. At the outset of a project directed at the synthesis of natural product derivatives of (**1a-c**) we sought a mild general method for the construction of these cyclic systems. The utility of phosphoranes in "non-classical" Wittig reactions, in which the carbonyl component is a carboxylic acid

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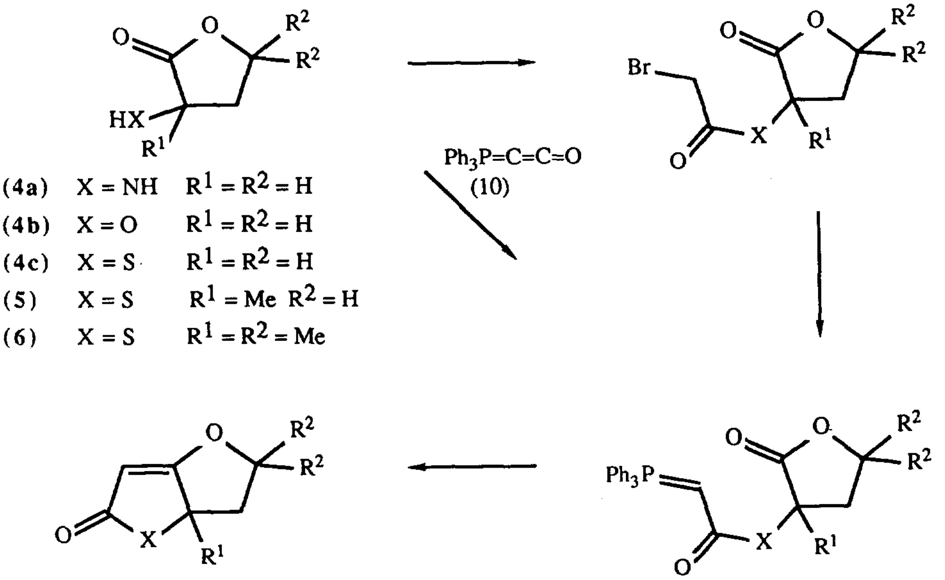
derivative such as an ester [4] or amide,[5] has been the subject of a number of reports in recent years and we undertook to examine the intramolecular reaction of phosphoranes with lactones as a general route to lactone derivatives of (**1a-c**).

γ-Lactones were chosen as starting materials because of their ready availability and their relatively reactive carbonyl groups. Compound (**4a**) is commercially available whereas (**4b**), (**4c**), (**5**) and (**6**) were synthesised from the the appropriate α-bromo-γ-butyrolactones.[6,7] Each was then converted into its bromoacetyl derivative ($BrCH_2COBr$, Et_3N, -20°) and phosphonium bromides of these were prepared by reaction with triphenylphosphine; treatment with base (DBN) was presumed to give rise to the corresponding ylides which cyclised under the reaction conditions to furnish the desired lactones (**7a-c**), (**8**), and (**9**). An alternative approach to formation of the ylides and thus the lactones was by reaction of (**4a-c**), or (**5**) with triphenylphosphoranylideneketene (**10**),[8,9] (Scheme).



(4a) X = NH $R^1 = R^2 = H$
(4b) X = O $R^1 = R^2 = H$
(4c) X = S $R^1 = R^2 = H$
(5) X = S $R^1 = Me$ $R^2 = H$
(6) X = S $R^1 = R^2 = Me$

(7a) X = NH $R^1 = R^2 = H$
(7b) X = O $R^1 = R^2 = H$
(7c) X = S $R^1 = R^2 = H$
(8) X = S $R^1 = Me$ $R^2 = H$
(9) X = S $R^1 = R^2 = Me$

Scheme

The results by both methods and in each case are tabulated (Table). Yields from (**10**) were low, apparently because of its sluggish reaction with the amine, alcohol and thiol nucleophiles which decomposed upon prolonged heating; this approach did however bypass the formation and isolation of the bromoacetyl and phosphonium intermediates.

Table

Product[10]	% Yield from Phosphonium	Conditions (Δ = reflux)	% Yield from (**10**)	Conditions (Δ = reflux)
(**7a**)[11]	72	THF/Δ/9h	35	$PhCH_3$/Δ/8h
(**7b**)[12]	35	THF/Δ/3h	30	$PhCH_3$/80°/66h
(**7c**)[13]	30	$CHCl_3$/Δ/16h	20	$PhCH_3$/Δ/66h
(**8**)[14]	42	THF/Δ/16h	10	$PhCH_3$/70°/16h
(**9**)[15]	56	dioxan/Δ/20h	not attempted	

The novel intramolecular reactions of these phosphorane derivatives of γ-lactones therefore provides a mild convenient route to lactones of tetronic, thiotetronic and tetramic acid derivatives in acceptable yields. The chemistry and synthetic utility of these compounds are currently being explored.

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10. All products are new compounds and gave satisfactory microanalytical data.
11. (**7a**), m.p. 119-121°; i.r. ($CHCl_3$), 3420, 1690, 1640 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$), 1.96 (1H, m), 2.42 (1H, m), 4.45 (1H, m), 4.61 (1H, m), 4.80 (1H, dd, J = 9 Hz, 9 Hz), 5.02 (1H, s), 6.35 (1H, br.s).
12. (**7b**), m.p. 51-53°; i.r. ($CHCl_3$), 1760, 1650 cm^{-1}; ^{1}H n.m.r. ($CDCL_3$), 2.16 (1H, m), 2.56 (1H,