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ADDITION OF 1-METHOXY-1-BUTEN-3-YNE TO LACTONES: SYNTHESIS OF SUBSTITUTED SPIROKETALS[1]

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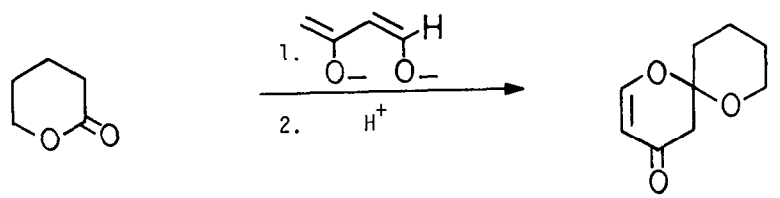
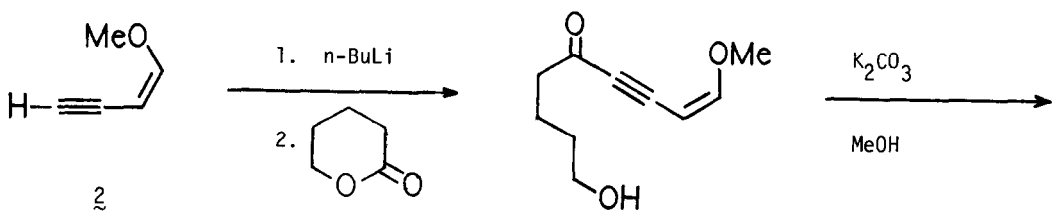
Abstract
A method for the preparation of a variety of substituted spiroketals from lactones and 1-methoxy-1-buten-3-yne has been developed.

In conjunction with our studies on the total synthesis of spiroketal containing natural products including the milbemycins[2] and the avermectins,[3] we required a short, efficient synthesis of spiroketal systems of general structure 1. These unsaturated spiroketals have great potential as intermediates in the synthesis of a wide variety of important spiroketal containing natural products. We describe here a method for the preparation of several systems similar to 1 from 1-methoxy-1-buten-3-yne 2[4] and the appropriate lactone precursor.

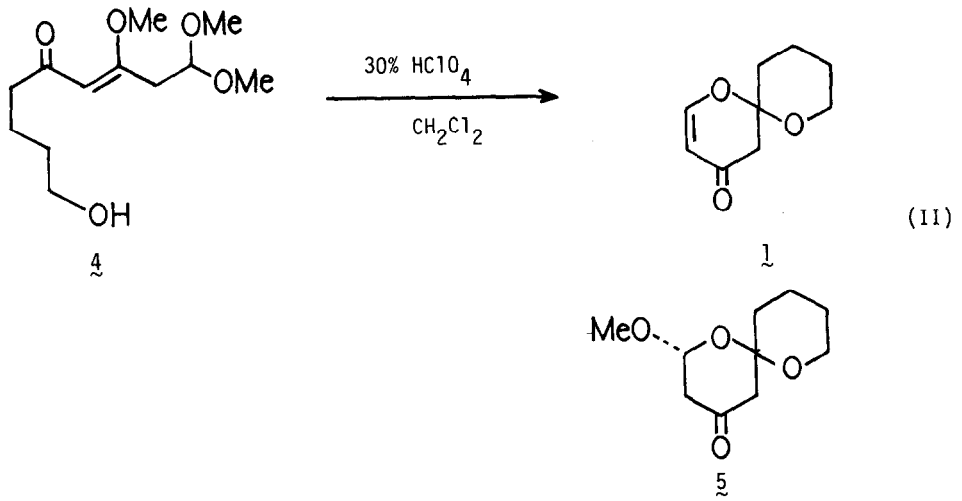
Preliminary efforts to generate 1 from the addition of formylacetone dianion[5] to δ-valerolactone followed by acid catalyzed cyclization (Equation I), similar to the method of Barrett,[6] met with disappointing results. We anticipated that 2 would serve as an equivalent to formylacetone dianion and might be handled more easily. In fact, addition of δ-valerolactone to a solution of the lithium acetylide of 2 in tetrahydrofuran at -78 °C resulted in the isolation of keto-alcohol 3 in 98% yield.



1 (I)



2 3 (II)



4 1 5 (II)

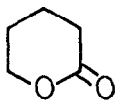
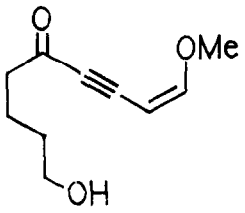
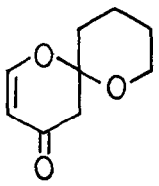
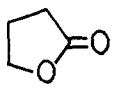
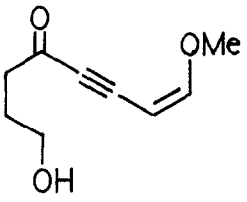
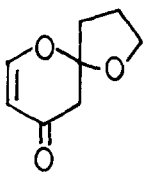
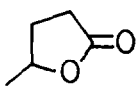
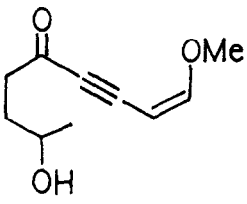
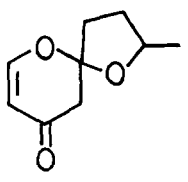
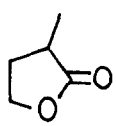
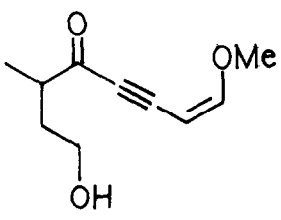
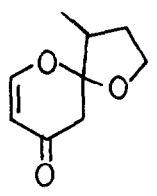
Conversion of 3 into spiroketal 1 can be accomplished by two different procedures. Method A: Treatment of keto-alcohol 3 with catalytic potassium carbonate in methanol produced trimethoxy ketone 4. Initial attempts directed toward conversion of 4 into spiroketal 1 in a magnetically stirred, dichloromethane-30% aqueous perchloric acid biphase produced a 1:1 mixture of 1:5. It was subsequently determined that more rapid stirring (mechanical stirrer) produced only 1, apparently as a result of more efficient contact between the aqueous and organic phases. Method B: Alternatively, a one-step conversion of 3 to 1 was effected by directly treating 3 with 30% $HClO_4$-CH_2Cl_2, but typically the yields for the one-step procedure were somewhat lower.

We have utilized these procedures to carry out the synthesis of a number of variously substituted spiroketals and the results are shown in Table I. A typical procedure for these transformations follows.

Addition of 1-Methoxy-1-buten-3-yne 2 to Lactones: A solution of n-butyllithium (10.6 mL, 27.4 mmol, 2.6 M in hexane) was added dropwise under nitrogen to a stirred, cooled (-78 °C) solution of 2 (2.25 g, 27.4 mmol) in 50 mL of dry tetrahydrofuran. Stirring was continued for 1 h whereupon δ-valerolactone (27.4 mmol) in 2 mL tetrahydrofuran was added rapidly. After stirring for 1 h at -78 °C the mixture was quenched with saturated ammonium chloride, warmed to 0 °C and diluted with ether. The organic layer was dried and concentrated to provide 4.89 g (98%) of the keto alcohol 3 as a clear yellow oil. 250 MHz ^1H NMR ($CDCl_3$, δ) 1.45-1.85 (m, 4H); 2.61 (t, J=7.1 Hz, 2H); 2.74 (br s, 1H); 3.63 (t, J=6.3 Hz, 2H); 3.87 (s, 3H); 4.67 (d, J=6.4 Hz, 1H); 6.60 (d, J=6.4 Hz, 1H).

Spiroketal 1; Method A: A cooled (0 °C) solution of potassium carbonate (0.38 g, 2.74 mmol) and keto-alcohol 3 in 50 mL methanol was stirred for 16 h. The reaction mixture was concentrated to 10 mL, diluted with ether, filtered, dried, and concentrated to give crude ketone 4. This material was dissolved in 30 mL dichloromethane, the solution was cooled to 0 °C, and 30 mL of precooled 30% perchloric acid was added with vigorous stirring (mechanical stirrer). After stirring for 10 min, the organic layer was neutralized with saturated sodium bicarbonate, dried and con-

TABLE[a]

Lactone	Keto Alcohol	(YD)	Spiroketal	(Method, YD)[b]
		(98)		(A, 86) (B, 58)
		(69)		(A, 53) (B, 69)
		(97)		(B, 60)
		(89)		(B, 50)

[a]All spiroketals gave satisfactory C,H combustion analyses and consistent spectral data including 250 MHz ^{1}H NMR.

[b]Yields are for isolated purified material.

centrated to afford the essentially pure spiroketal 1 (3.88 g, 86%). 250 MHz ^{1}H NMR ($CDCl_3$, δ) 1.5-2.1 (m, 6H); 2.61 (m, 2H); 3.70 (m, 2H); 5.46 (d, J=6.0 Hz, 1H); 7.22 (d, J=6.0 Hz, 1H).

Method B. The exact procedure used for the cyclization of ketone 4 above was carried out directly on keto-alcohol 3 to provide the spiroketal 1.

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1. Financial support from the National Institutes of Health (AI-19544-01) and the Merck, Sharp, and Dohme Company is gratefully acknowledged.
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