A New Method for the Preparation of γ-Hydroxy Ketones: a Formal Total Synthesis of (±)-Lanceol

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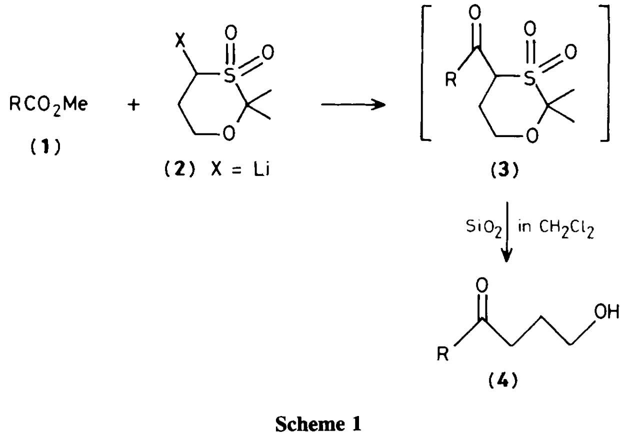
The reaction of methyl esters with 2,2-dimethyl-4-lithio-1,3-oxathiane 3,3-dioxide followed by treatment with silica gel affords γ-hydroxy ketones.

Recently, we reported a three-carbon unit elongation of aldehydes to provide γ-hydroxy ketones in a two-step sequence involving the addition of 2,2-dimethyl-4-lithio-1,3-oxathiane 3,3-dioxide (**2**, X = Li) followed by Jones oxidation.[1] We now report an improved method for the preparation of γ-hydroxy ketones using (**2**, X = Li) as a synthetic equivalent of the γ-hydroxypropyl anion and describe the synthetic use of this method.

As shown in Scheme 1, the reaction of (**2**, X = Li) with methyl esters proceeds smoothly in tetrahydrofuran (THF) to afford labile β-keto sulphones (**3**). The solution of the crude keto sulphone was treated with silica gel in dichloromethane for 30 min. Evaporation of the solvent under reduced pressure followed by dry column chromatography gave pure γ-hydroxy ketones (**4**).† Though an active ester such as (**5**) and an active amide such as (**6**) can be employed in this reaction (runs 10 and 11 in Table 1), methyl esters give satisfactory results in general. It should be noted that 2 mol equiv. of base to 1 mol equiv. of (**2**, X = H) or 2 mol equiv. of (**2**, X = Li) are necessary for this reaction because the product (**3**) has a more acidic proton than the starting sulphone (**2**, X = H).

The formal total synthesis of (±)-lanceol (**10**) illustrates the synthetic use of this method. The cycloadduct (**7**)[2] obtained



Scheme 1

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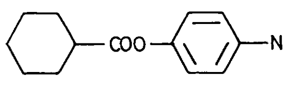
† Satisfactory spectroscopic and analytical data were obtained for all new compounds reported.

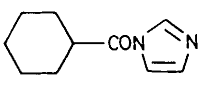
Table 1. Preparation of γ-hydroxy ketones.[a]

Run	Substrate	% Yield of (**4**)
1	(**1**, R = Pr^i)	59
2	(**1**, R = n-C_5H_{11})	64
3	(**1**, R = n-C_7H_{15})	77
4	(**1**, R = n-C_9H_{19})	78[b]
5	(**1**, R = n-$C_{13}H_{27}$)	53
6	(**1**, R = Ph)	61
7	(**1**, R = *p*-MeC_6H_4)	78
8	(**1**, R = *p*-$MeOC_6H_4$)	89[b]
9	(**1**, R = cyclohexyl)	80
10	(**5**)	68
11	(**6**)	75

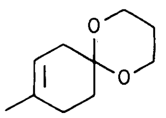
[a] THF solution of the ester was added to 2 mol equiv. of (**2**, X = Li) in THF at −78 °C. [b] To an equimolar solution of the substrate and (**2**, X = H) was added 2.1 equiv. of LDA in THF.



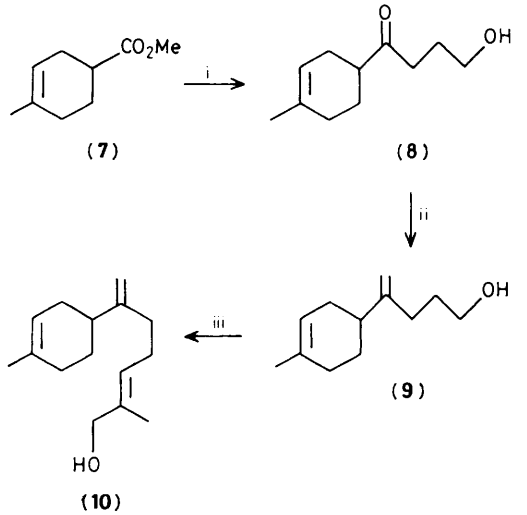
(**5**)



(**6**)



(**11**)



Scheme 2. *Reagents:* i, (**2**, X = H), lithium di-isopropylamide (LDA) (2.1 equiv.), 87%; ii, $Ph_3P{=}CH_2$, dimethyl sulphoxide (DMSO), 78%; iii, ref. 3.

from the acid-catalysed Diels–Alder reaction of isoprene with methyl acrylate was converted into the γ-hydroxy ketone (**8**) in 87% yield by the present method. The Wittig reaction using (**8**) afforded diene (**9**) in 78% yield, which has been converted into (±)-lanceol previously.[3] Recently, the diene (**9**) has been prepared from (**11**) *via* four steps in 22% overall yield.[4]

Received, 26th September 1986; Com. 1380

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