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CYCLISATION *vs* ACYL MIGRATION OF α-ALLYL LACTONE DERIVED ANION : SYNTHESIS OF SPIRO[4,5]DEC-2-ENE-1,6-DIONES

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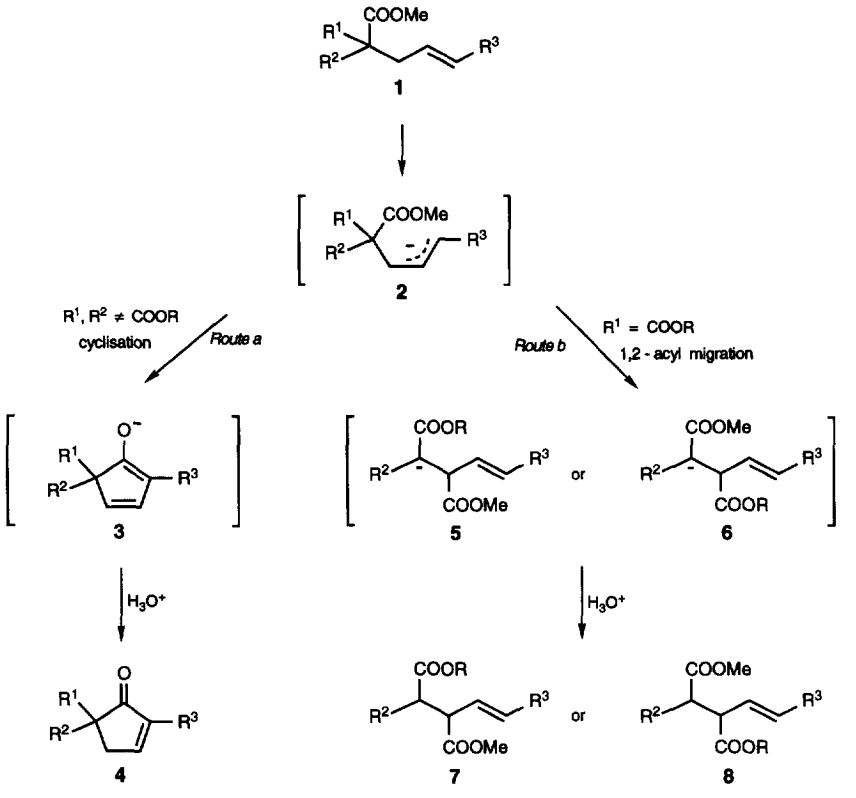
Abstract : Directed by substituent R^1, the α-allyl-γ-butyrolactone **9** either undergoes cyclisation to give the alcoholic cyclopentenone **12** or 1,2-acyl migration to give **13**, when subjected to treatment with LDA in THF/TMEDA. An effective strategy to nullify this directive influence, and dictate cyclisation, is exemplified in a model synthesis of spiro[4,5]dec-2-ene-1,6-dione **19** by a one-pot tandem cyclisation - elimination process starting from **16**.

Since our initial report of the base catalysed cyclisation of methyl 2,2-disubstituted 4-pentenoate, e.g. **1**, leading to cyclopentenone **4**,[1] we have found the method to be extremely useful in applications where α-methylene cyclopentenones (e.g. **4**; R^1, R^2 = methylene)[2] including various naturally occurring cyclopentenoid antibiotics,[3] e.g. methylenomycin A and deepoxy-4,5-didehydromethylenomycin A,[4] methylenomycin B,[2] and sarkomycin[5] have been synthesized. Evidently involving an intramolecular acylation of intermediate anion **2** the reaction provides dienolate **3**, and after protonation, cyclopentenone product **4** (Scheme 1, *route a*). Although trapping of dienolate **3** has been demonstrated with various electrophiles attempts to trap the allyl anion **2** have not been successful, which indicates a fast cyclisation step.

Nevertheless, when either of the substituents R^1 or R^2 is an ester group no cyclised product can be obtained from **1** under the standard cyclisation conditions, the reaction providing, instead, **7** (or **8**), arising from a 1,2-migration of the ester group (*route b* in Scheme 1).[6] Thus treatment of the open chain allyl diesters **1***a-c* (*a*, R^1 = COOMe, R^2 = Me, R^3 = Ph; *b*, R^1 = COOMe, R^2 = Ph, R^3 = Me; *c*, R^1 = COOMe, R^2 = R^3 = Ph) with LDA (3 equivalents, excess) in THF-TMEDA = 10 : 1 at -78° followed by stirring at room temperature overnight affords the corresponding ester migration products **7***a-c* (R = Me) in 69%, 75% and 81% yields respectively.[7] Further insight into the mechanism is obtained from the application of the reaction to allyl lactones **9**, as shown in Schemes 2

Preparation of the starting allyl-γ-butyrolactone **9** is straightforward by allylation, then lactonization (using ethylene oxide) of methyl alkylacetate (for **9***a-d*) or dimethyl malonate (for **9***e-h*). LDA treatment of **9** leads to either the cyclisation product **12**, or the acyl migration product **13**, depending upon the nature of substituent R^1. In line with the foregoing mechanistic deductions the alcoholic cyclopentenone **12** is obtained (*via* **10**) when R^1 is methyl (entry *a*, Scheme 2) or phenyl (entries *b-d*), whereas, the reaction follows an altogether different path,

Scheme 1

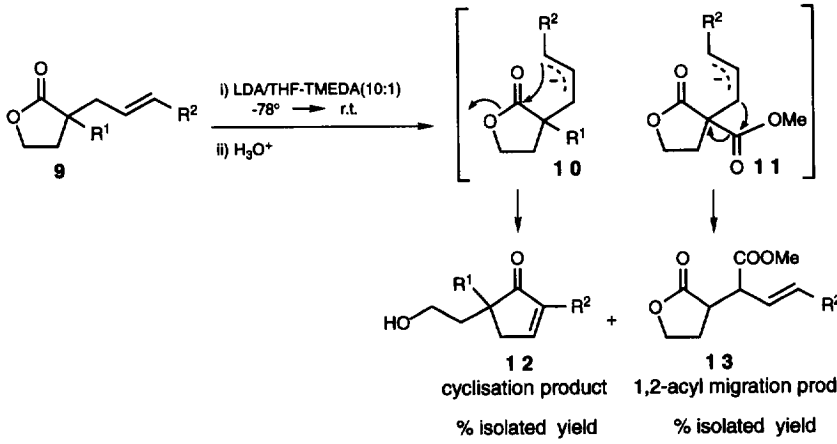


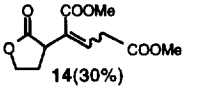
when R^1 is COOMe (entries *e-h*), a 1,2-acyl migration (**11**) taking place to give the corresponding ester enolate and finally the observed product **13** (or its isomer **14**, when $R^1 = R^2 =$ COOMe.).

A significant observation here is that the acyl migration reaction is both regio- and acyl specific, that is, no product arising from a 1,4-acyl migration of anion **11** can be detected, nor is there any sign of a 1,2-migration of the lactone carbonyl moiety which would result in a lactone ring expansion. This latter point is rationalized in terms of the less favourable transition state involving the comparatively strained bicyclo[3.1.0]hexane system.

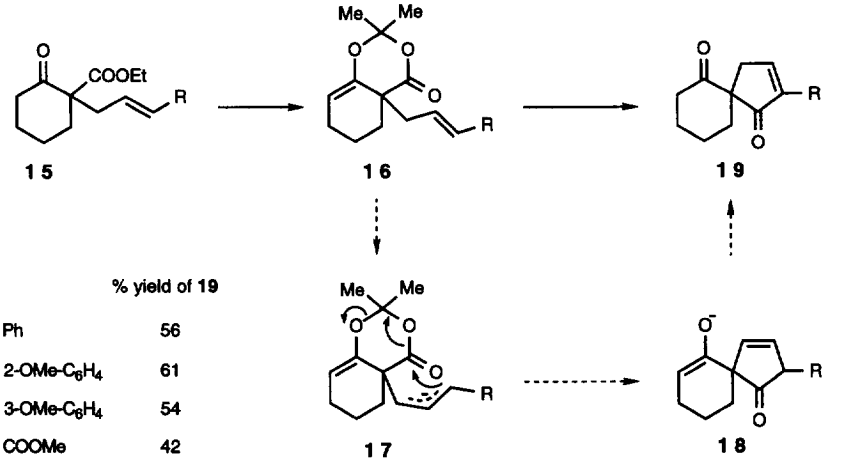
In seeking to extend the scope of the cyclisation reaction to accommodate diacyl substrates, it is essential that acyl migration is suppressed. This can be accomplished in the case of **15** by masking the keto group as shown in **16**, which effectively nullifies its influence and dictates cyclisation. Thus a convenient synthesis of spiro-diones can be achieved as demonstrated in the straightforward synthesis of spiro[4,5]dec-2-ene-1,6-diones as shown in Scheme 3. Allyl-lacto-acetal **16**, prepared from commercial ethyl 2-cyclohexanonecarboxylate,[8] is treated with an LDA/ THF-TMEDA base system whereupon tandem cyclisation - elimination takes place in a single operation to provide the desired **19** *via* **17** and **18**. Even though yields of the product **19** are not spectacular the ready preparation of starting material **16** coupled with the ease of subsequent operation makes the overall methodology a very attractive route in comparison to existing methods.[9]

Scheme 2



a, R^1 = Me, R^2 = Ph	68	-
b, R^1 = Ph, R^2 = H	47	-
c, R^1 = Ph, R^2 = Me	54	-
d, R^1 = R^2 = Ph	71	-
e, R^1 = COOMe, R^2 = H	-	61
f, R^1 = COOMe, R^2 = Ph	-	62
g, R^1 = COOMe, R^2 = 3-OMe-C_6H_4	-	66
h, R^1 = R^2 = COOMe	-	 14(30%)

Scheme 3



	% yield of **19**
R = Ph	56
R = 2-OMe-C_6H_4	61
R = 3-OMe-C_6H_4	54
R = COOMe	42

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