Extension of the Proline-Catalysed Asymmetric Annelation to Diketones. A New Case of Kinetic Resolution

Claude Agami,* Jacques Levisalles, and Hubert Sevestre

Laboratoire de Chimie Organique associé au CNRS, Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France

Asymmetric Robinson annelation of racemic diketones leads to enantiodifferentiation which depends on the presence or the absence of an angular methyl group.

The amino acid-catalysed asymmetric cyclization[1] of several optically inactive triketones, *e.g.* (1), has been studied but is unprecedented, to our knowledge, with racemic diketones, *e.g.* (2).

Such a reaction could provide information about the mechanism of enantioselection which is still rather obscure. Inspection of the diketone (2) shows that the cyclic carbonyl groups of the *S* and *R* enantiomers correspond respectively to the *pro-R* and *pro-S* carbonyl groups of the triketone (1). As it is well known that the (*S*)-proline-catalysed asymmetric annelation of substrates similar to (1) involves the *pro-R* carbonyl group, it could be predicted that the compound (*S*)-(2) should cyclize faster than the (*R*)-(2) enantiomer.

This was confirmed in the following way. Diketone (±)-(2)

(1)

(R)-(2)

(S)-(2)

(3)   (4)

(5)   (6)

(7)

Scheme 1

(1)   (S)-(2)

(R)-(4)

Scheme 2
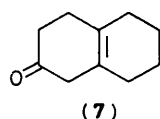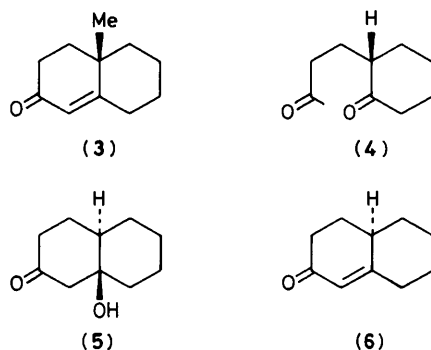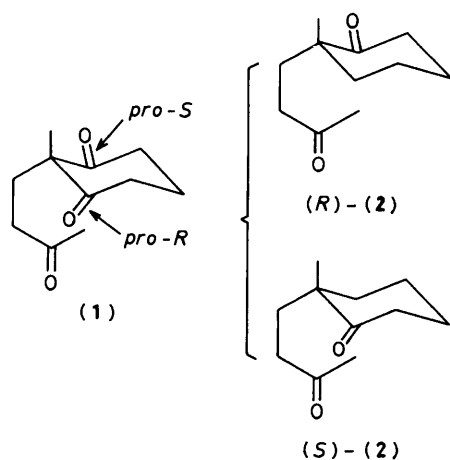
(0.5 g), when treated (1 h, 65 °C) with (S)-proline (0.19 g) in dimethylformamide (DMF) (6 ml), afforded the cyclized enone (S)-(3) {[α]$_D$ + 84° (c 0.7, dioxane), 0.11 g} along with the recovered (2) {[α]$_D$ + 16° (c 0.7, dioxane), 0.31 g}. The 4S configuration and the optical purity (43%) of enone (+)-(3)† were determined by comparison with its reported optical rotation.[2] The recovered diketone (+)-(2) was thus the less reactive enantiomer; its R configuration was deduced by comparison with (+)-(3), necessarily deriving from (S)-(2).

On the other hand, the ketone (±)-(4) which is the unmethylated analogue of (±)-(2) underwent an opposite enantioselective cyclization. A DMF solution (12 ml) of (±)-(4) (1 g) was treated (90 h, room temp.) with (S)-proline (0.38 g). Four compounds were isolated: i, the recovered diketone (4) {[α]$_D$ − 2° (c 2, ethanol), 0.33 g}; ii, the ketol (5)‡ {[α]$_D$ − 43° (c 0.5, ethanol), 0.30 g}; iii, the conjugated enone (R)-(6) {[α]$_D$ − 3° (c 1, ethanol), 0.31 g} iv, the unconjugated enone (7) (0.02 g). The absolute configuration of the resulting enone (6) was established by comparison of the sign of its optical rotation with that of the reported literature value[4] [the presence of the unconjugated isomer (7)

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† It was checked that enone (+)-(3) and ketol (−)-(5) are optically stable under the reaction conditions by sampling their optical activities at various reaction times.

‡ Racemic ketol (5) (ref. 3) and (−)-(5) exhibited identical i.r. and ¹H n.m.r. spectra.
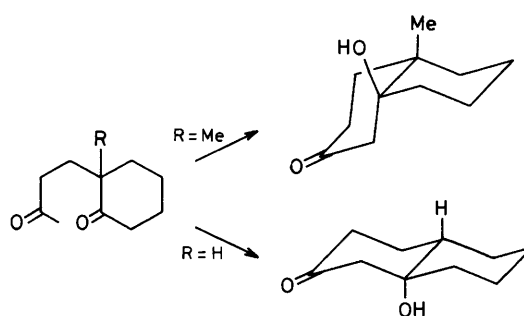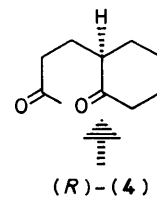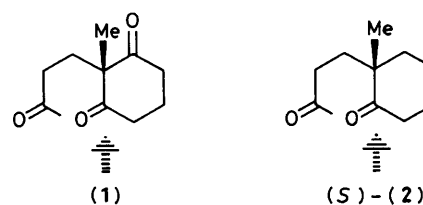
gives evidence of a partial racemization of (R)-(6)]. Compounds (−)-(5)† and (−)-(4) were thus determined to be 4aR, 8aS, and S respectively as formulated. Accordingly, ketol (−)-(5) was dehydrated (toluene-p-sulphonic acid in benzene) to (−)-(6) and (7). The optical purity of ketol (5) (65% optical purity) was known from the measurement of the optical rotation of a sample of enantiomerically pure (−)-(5) {[α]$_D$ −66° (c 0.5, ethanol)} obtained by crystallization from acetone at −40 °C (m.p. 171 °C); its enantiomeric purity was ascertained by differential scanning calorimetry.[5]

Therefore in the case of compound (4) the R enantiomer is the most reactive and its steric requirements around the cyclic carbonyl group correspond, as aforesaid, to those of the unreactive pro-S carbonyl group in the often studied meso triketones. It is worth noting that there is an additional beneficial factor, namely the interconversion between (S)-(4) and (R)-(4), equation (1).

$$(S)\text{-}(6) \xleftarrow{k_S} (S)\text{-}(4) \rightleftharpoons (R)\text{-}(4) \xrightarrow{k_R} (R)\text{-}(6) \quad k_S < k_R \quad (1)$$
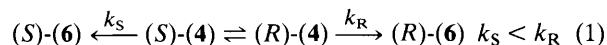
The stereochemistry of the intermediate ketols must be taken into account in order to explain this discrepancy. It has already been reported[3,6] that the cyclization, under usual achiral conditions, of such diketones takes two different pathways according to the nature of the angular group (Scheme 1).

Without scrutinizing the details of the enantiodifferentiation mechanism, it can merely be stated that the same conformational requirements which favour the α attack on the pro-R carbonyl group in (1) or the S enantiomer of (2) should also favour α attack on the R enantiomer of (4) (Scheme 2).

Concerning the stereoselective formation of cis or trans ketols (Scheme 1), Deslongchamps[7] recently pointed out that: i, the cis ketol formation from methylated diketones can be simply explained by the presence of the methyl group on the β

side of the molecule; ii, the α attack on unmethylated diketones is very puzzling and could be the consequence of a stereoelectronic control. *trans* decalines are actually known to be more stable than their *cis* isomers[8] owing to *gauche* interactions; therefore the same unfavourable interactions could prevent the approach leading to the *cis* ketols. A conformational energy calculation (SCRIPT method[9]) bears out this statement: the *trans* ketol (5) is energetically favoured by 1.7 and 1.8 kcal mol^{-1} (1 kcal = 4.18 kJ) over the steroid and the non-steroid *cis* ketols respectively.

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