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si-Enantioface Selectivity in (*S*)-Proline-catalysed Asymmetric Annelation

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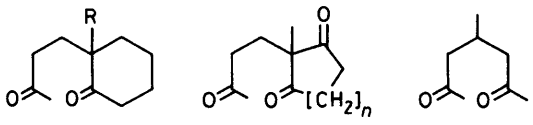
The cyclisation of an acyclic diketone shows that the selective attack onto a *si* face is a stereochemical link between various enantioselective proline-catalysed annelations.

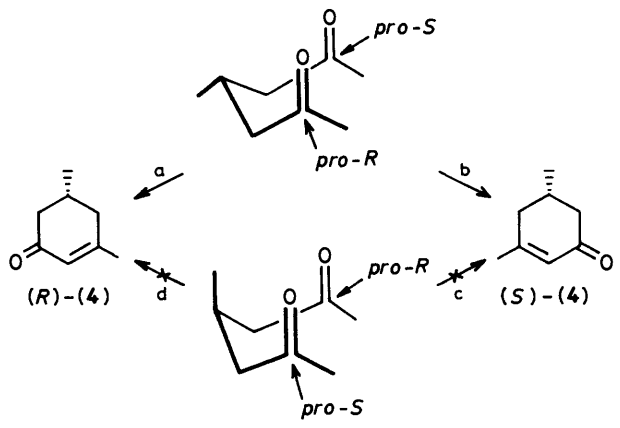
Recently[1] we demonstrated that the overall stereochemical outcome of the proline-catalysed cyclisation of the racemic diketones (**1**) is related to the well known behaviour displayed by prochiral triketones (**2**).[2]

Cyclisations of the acyclic diketone (**3**) could provide more information as the steric effects operating in the ketolisation transition state are liable to be uncomplicated, since the substrate is relatively simple. Moreover this reaction would be a further extension of the Hajos–Parrish asymmetric annelation.[3]

A dimethylformamide solution (6 ml) of 4-methylheptane-2,6-dione (0.5 g) was treated (48 h, room temperature) with (*S*)-proline (0.09 g). Silica gel column chromatography afforded 3,5(*R*)-dimethylcyclohex-2-enone (**4**) (0.33 g, 75%) {$[\alpha]_D$ −59° (*c* 2, chloroform), lit.[4] −138.4°, optical purity: 43%}. The optical purity of the enone (−)-(**4**) was 7% when (*S*)-phenylalanine was used instead of (*S*)-proline.



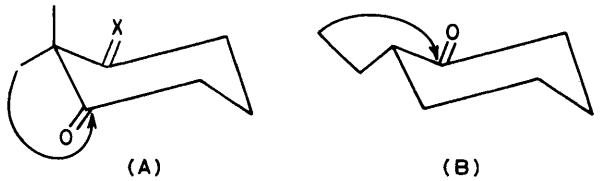
(**1**) R = H, Me (**2**) *n* = 1,2 (**3**)



Scheme 1

A carbonyl group acts as the electrophile during the ketolisation of (**3**) and two enantiomeric products can be obtained (Scheme 1). Thus the *R* enone (−)-(**4**) arose from a nucleophilic attack onto the *pro-S* carbonyl group. The four possible pathways are shown in the scheme, where the relative positions of the carbonyl groups are set as in the usual cyclic substrates. The nucleophilic attack onto the *pro-S* carbonyl group can occur *via* paths a or d (*si* or *re* face attack respectively) whereas the corresponding attack onto the *pro-R* carbonyl group can follow paths b or c (*re* or *si* face attack respectively). Condensations occurring *via* paths c or d are not expected owing to severe 1–3 diaxial interactions. These are due to the pre-axial methyl group in the transition states interacting with a proline-activated carbonyl group.[2]

Scheme 1 suggests that the former experimental result implies a nucleophilic attack onto the *si* face of the *pro-S* carbonyl group (path a). This enantioface selectivity links together all the (*S*)-proline-catalysed asymmetric cyclisations reported so far[1—3] as shown by (A) and (B) where the curved arrows represent the alkylcarbonyl side chains: a selective attack onto a *si* face occurs during the 'underside' annelation of a methylated triketone (A : X = O) or of a diketone (A: X = H_2) as well as for the annelation of an unmethylated diketone from above [see (B)].



(A) (B)

Therefore the original Hajos–Parrish reaction which dealt with prochiral triketones has great versatility; the *si* face selectivity is common to all the various stereochemical results previously reported and should be taken into account in any mechanistic model proposed.

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