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Asymmetric Synthesis without solvent

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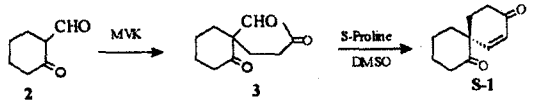
Abstract: Asymmetric syntheses of the diketones **S-1**, **S-6**, and **S-10** from the precursors **3**, **5** and **8** respectively have been carried out in the absence of solvent employing S-proline as chiral auxiliary. Copyright © 1996 Elsevier Science Ltd

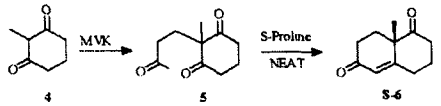
The spirodione **S-1** has previously[1] been obtained in our laboratory by an enantioselective cyclization of (±)-**3** obtained by annelation of 2-formyl cyclohexanone with methyl vinyl ketone.



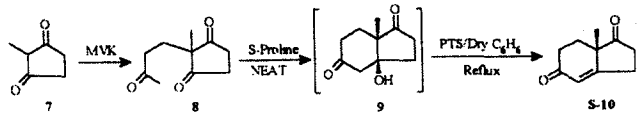
2 **3** **S-1**

The cyclization carried out in DMSO solvent using catalytic amounts of S-proline, gave **S-1** in 70% chemical yield[2] and 22.4% enantiomeric excess. With a view to improving these yields, (±)-**3**- a liquid at room temperature - was stirred with a catalytic amount of S-proline at room temperature under nitrogen atmosphere without any solvent. The progress of the reaction was monitored by following the increase in absorption at 227-229 nm characteristic of **S-1** at different intervals and the reaction was terminated when UV absorption indicated 50-65% conversion to **S-1**. Extraction with CH_2Cl_2 followed by washing with water furnished a liquid which was chromatographed (Silica gel 230-400 mesh, 7% Ethyl acetate/hexane) to give **S-1** as a pale yellow liquid in 49-58% yield. The PMR spectrum of this liquid product was identical with that of an authentic sample[1] but with $[\alpha]^{25}_D$ + 3.42 (C, 7.5 $CHCl_3$). The e/e of this product is 42.56% based on the e/e value 23.4% of the product with $[\alpha]^{25}_D$ + 1.8 obtained earlier.[1,2] This represents a two-fold improvement on the literature procedure using DMSO as solvent. The reaction period is also shortened in the present procedure conducted in the "NEAT", without any solvent.

Some chiral Michael additions have been reported recently[3] using phase transfer catalysts in the absence of solvents. The use of proline or any other amino acid in a solid-liquid phase reaction in the absence of solvents to effect an asymmetric synthesis is unprecedented. Solvents, particularly polar aprotic solvents are generally believed[4] to be necessary media for effecting asymmetric syntheses. Since our findings indicated that asymmetric induction occurred even in the absence of solvent, it was of interest to extend our "NEAT" methodology to the cyclization of the prochiral triones **5** and **8** respectively.



4 **5** **S-6**



7 **8** **9** **S-10**

These triones could be obtained as liquids by reacting diones **4** and **7** respectively with methyl vinyl ketone in aqueous solution as described in literature[5,6]. Their cyclizations to **S-6** and **S-10** are well documented and involve the use of aprotic solvents.

In the present study, the trione was stirred with varying amounts (0.05 to 0.43 equivalent) of S-proline (dried over anhydrous $CaCl_2$) under nitrogen atmosphere for different periods and the reaction mixture worked up and the product purified chromatographically as in the case of dione **S-1**. The progress of the reaction was monitored by following the UV absorptions periodically as described by Spencer *et al.*[7] The trione **8** was also reacted similarly with S-proline; the product in this case was the ketol **9** which without further purification was refluxed for 15 min. with PTS in dry benzene before making the UV measurement and before the final chromatographic purification. Table I gives details of conditions employed and results. The identity of chromatographed **S-6** and **S-10** was established by

IR and PMR. The e/e of the products was calculated on the basis of the reported[5,6] specific rotations of the enantiomerically pure products.

From Table I, it is seen that the best reaction conditions involve the use of 0.26 equivalents of catalyst and a reaction period of 67h at room temperature to get S-6 in 49% chemical yield with 62.5% enantiomeric excess. The use of 0.05 equivalent of catalyst at room temperature reduces the chemical yield to 33% but the enantiomeric purity is about the same (S. No. 3). Increase in reaction time or temperature leads to less enantiomerically pure products (S. No. 5,7). The reaction does not proceed in the temperature range 0-10°C (S. No.8). For obtaining S-10, the optimum conditions were 0.05 equivalent of catalyst, a reaction time of ca 90h for 63-64% chemical yield with 60-68% enantiomeric excess (S. No. 9, 10). No attempts were made to obtain 100% enantiomerically pure diones; the liquid product S-6 with 60-65% e/e could be used[2] for ethynylation at the saturated carbonyl group to give exclusively (+)-1R, 8a S 1-ethynyl-1-hydroxy-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a octahydro naphthalene.[9]

Table I : Effect of stoichiometry, temperature and time on chemical yield and enantiomeric excess

S. No.	Substrate	Wt. of Substrate g (mole)	Amount of S-proline[(a)] mg (equiv.)	Temp.	Time h	Product	Yield from UV [(b)] (%)	e/e of product[(c)] (%)	Isolated yield (%)
1.	3	4 (0.02)	120 (0.05)	RT	40	S-1	65.6	39.8	58
2.	3	9.8 (0.05)	290 (0.05)	RT	66	S-1	50.2	42.56	49
3.	5	0.98 (0.005)	(*) 30 (0.05)	RT	68	S-6	39.3	64.7	33
4.	5	0.98 (0.005)	155 (0.26)	RT	67	S-6	56	62.5	49
5.	5	3 (0.015)	75 (0.43)	RT	111	S-6	53.2	55.5	47
6.	5	0.98 (0.005)	575 (1.00)	RT	67	S-6	41.5	50.0	34
7.	5	0.98 (0.005)	20 (0.04)	50°C	55	S-6	42	38.4	34
8.	5	0.98 (0.005)	35 (0.06)	0-10°C	120	S-6	Reaction did not proceed		
9.	8	1.82 (0.01)	55 (0.05)	15-20°C	88	S-10	74	60.18	66
10.	8	1.82 (0.01)	55 (0.05)	20-25°C	90	S-10	70.6	68.4	63

(*) Molecular sieves 4 Å was added; (a) Recrystallised S-Proline, $[\alpha]^{25}_D$ - 82 (C,4.4. water) was used

(b) For S-1 $\lambda^{ethanol}_{max}$ 227-229nm, ε,7740; For S-6 $\lambda^{ethanol}_{max}$ 242nm. ε,12,500; For S-10 $\lambda^{ethanol}_{max}$ 233nm, ε.11.540

(c) For S-1 $[\alpha]^{25}_D$ + 1.8 (C,7.5, $CHCl_3$), (e/e, 23.4%); For S-6 $[\alpha]^{25}_D$ + 100 (C,1.461, C_6H_6) (e/e, 100%); For S-10 $[\alpha]^{25}_D$ + 367 (C,1.0, C_6H_6)(e/e. 100%)

The asymmetric induction observed in our experiments may be considered as evidence of a solid-liquid topochemical reaction. We consider this unlikely since in the case of the trione 8 at least, stirring with S-proline gave a homogeneous phase. The mechanism of asymmetric induction is probably the same as has been invoked earlier[8] for the same reactions conducted in solvent. In this mechanism hydrogen bonding is believed to play a key role. In the absence of solvent, the reaction mixture is viscous in our case and molecular motions must be restricted resulting in more effective hydrogen bonding and chiral recognition. Work is in progress to extend the "NEAT" technique to other asymmetric syntheses.

Acknowledgment

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