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Asymmetric one-pot Robinson annulations

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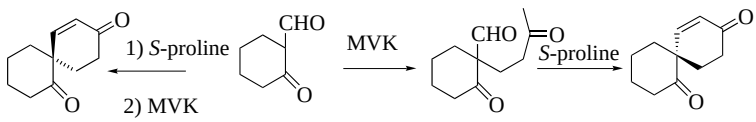
Abstract—One-pot syntheses of ketol *SS*-**5a**, enone *S*-**2** and optically active spiroenediones *S*-**14**, *R*-**7** and *S*-**15** are reported.

A recent publication[1] in this journal prompted us to present some related work[2] on asymmetric Robinson annulations. We reported earlier[3] that either of the enantiomers of cyclohex-2′-enespirocyclohexane-2,4′-dione (*S*- or *R*-**7**) can be obtained from 2-formylcyclohexanone using the same chiral auxiliary *S*-proline in DMSO, *S*-**7**, in a two-step reaction and *R*-**7** in a one-pot reaction.



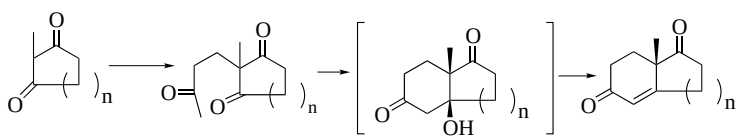
R-**7** *S*-**7**

The enantioselectivity was reversed in the above reactions when *R*-proline was used instead of *S*-proline. It was considered desirable to extend the above one-step methodology to the synthesis of *R*-isomers of the Wieland–Miescher ketones **1** and **2** since such a process, if successful, will be less costly than the literature procedures using the more expensive *R*-proline. The best literature procedures[4–6] for preparing (±)-**1**, (±)-**2** and their enantiomeric forms involve two-step processes in which the triones (**5** or **6**) are prepared first and then cyclodehydrated with achiral reagents to give the (±)-diketones or with *S*- or *R*-proline to give the *S*- or *R*-diketones, respectively (Scheme 1).

However, our expectations of synthesizing *R*-**1** and *R*-**2** using *S*-proline did not materialize; instead, convenient one-pot syntheses of the ketol *SS*-**5a**, dehydrated to *S*-**1** in a separate step, and diketone *S*-**2**, resulted.

1. One-pot synthesis of ketol *SS*-5a

A mixture of dione **3** (1.12 g, 0.01 mol) and *S*-proline (1.15 g, 0.01 mol) in dry DMSO (50 ml), degassed with nitrogen, was stirred for 6 h at 15–25°C under a nitrogen atmosphere followed by the dropwise addition of methyl vinyl ketone (MVK; 0.7 g, 0.01 mol). The reaction mixture was stirred for an additional period of 145 h and then poured into water (200 ml). The aqueous mixture was extracted with ethyl acetate (5×



3, n =1 **5**, n =1 *SS* -**5a**, n =1 *S* -**1**, n =1
4, n =2 **6**, n =2 *SS* - **6a**, n =2 *S* - **2**, n =2

Scheme 1.

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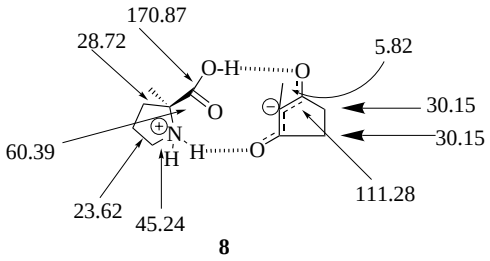

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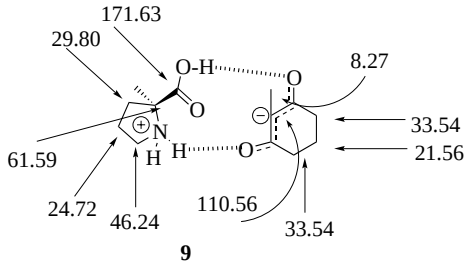

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200 ml). The combined organic extract was washed with brine, dried (anhyd. $MgSO_4$) and concentrated in vacuo to give the crude ketol *SS*-**5a** as a tan solid. This was refluxed in dry benzene (25 ml) with a pinch of PTS for 2 h to give a brown viscous liquid after washing with H_2O and removal of the solvent. Chromatography on silica gel (200–400 mesh) with $CHCl_3$ as eluant furnished several fractions; using TLC, the appropriate fractions were combined to give a viscous pale yellow material (yield: 65–70%, ee: 76.6%). This material was recrystallized from an ether–hexane (1:1) mixture after cooling to give colorless crystals of *S*-**1**, mp 66–66.5°C (60–65% chemical yield) and $[\alpha]_D^{25}$ +362.06 (*c* 1, C_6H_6), ee 98.6%.

The above methodology was applied to dione **4**, using dry DMSO or dry DMF as solvent and an equivalent amount of *S*-proline. After work-up, as above, a crude brown liquid was obtained. Chromatographic purification (silica gel, 25% EtOAc/hexane) furnished a less colored liquid, which on distillation in vacuo (115–120°C/0.05 mm) furnished *S*-**2** as a liquid in 68% chemical yield and 63% optical yield.

The same one-pot method in the presence of an equivalent amount of pyrrolidine and acetic acid instead of *S*-proline furnished a 70% yield of (±)-**2**, mp 48–9°C after chromatography and distillation. The 'neat' methodology of asymmetric synthesis[7] without solvent was applied to the above one-pot annulation. Table 1 summarizes the results obtained with and without solvent; both the optical and chemical yields were improved using solvent.

2. Mechanism of the one-pot reaction

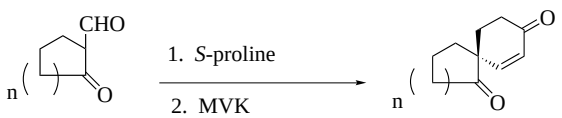
The above one-pot syntheses, particularly those carried out in a solvent, may be expected to involve initial formation of chiral enamines. With a view to getting evidence for such intermediates, we carried out ^{13}C NMR studies to follow the course of the one-step formation of ketol *SS*-**5a**.

Equivalent amounts of dione **3** and *S*-proline were mixed together in DMSO-d_6, allowed to stand for 6 h and then distilled MVK (1 equiv.) was added. ^{13}C NMR (400 MHz) spectra taken at regular intervals revealed that initially the insoluble proline forms the soluble complex **8**, which then reacts with MVK. Immediately after the addition of MVK, carbon signals are seen for trione **5**, ketol *SS*-**5a**, the soluble proline complex **8** and unreacted MVK. After 3 h the formation of ketol *SS*-**5a** is complete with no trace of MVK, trione **5** or complex **8**. Continued standing (up to 68 h) showed mainly ketol *SS*-**5a** with a trace of enone *S*-**1**. There was no evidence for the formation of any enamine intermediate. Complex **8** showed the carbon signals as indicated above. Evidently, the soluble proline complex gives the Michael adduct **5** known[6,8] to cyclize to ketol *SS*-**5a** with *S*-proline. The one-step reaction with the dione **4** was similarly monitored by taking the ^{13}C NMR spectra at regular intervals over a period of 22 h. Again, there was no evidence for the formation of an enamine; there was only evidence for the soluble complex **9**, which reacts with MVK to give the adduct **6**, known[5a,8] to cyclize to *S*-**2** in the presence of *S*-proline. The same mechanism is probably followed in the one-step processes carried out without solvent, though we have no experimental evidence.

3. One-step syntheses of optically active spiroenediones

We have extended the one-step methodology to annulation of a number of 2-formylcyclonones (Scheme 2), and obtained the optically active spiroenediones *S*-**14**, *R*-**7** and *S*-**15**. The reaction conditions and results are summarized in Table 1.

The annulations were carried out 'neat' as well as in dry DMSO. The chemical (48–52%) and optical yields (9–34%) were approximately the same. The product obtained from 2-formylcyclododecanone **13** turned out to be (±)-**16**, identical in mp and spectral properties with an authentic sample prepared according to the literature.[9] The spiroenediones were characterized by ^1H NMR, ^{13}CNMR, CD and elemental analysis. Their absolute configurations were deduced by comparison of the ORD curves with that of the diketone *S*-**2**. The



n = 1 , **10**
n = 2 , **11**
n = 3 , **12**
n = 8 , **13**

n = 1 , *S*-**14**
n = 2 , *R*-**7**
n = 3 , *S*-**15**
n = 8 , (±)**16**

Scheme 2.

Table 1. Stoichiometry, reaction conditions, chemical and enantiomeric yields

S. No.	Reactant	Reactant, g (mol)	*S*-Proline, g (mol)[a]	MVK, g (mol)	Solvent	Time (h)	Temp. (°C)	Product	ee[b] (%)	Yield (%)
1	**3**	1.12 (0.01)	1.15 (0.01)	1.4 (0.02)	DMF	145	15–20	*S*-**1**	76.6[c]	70
2	**3**	1.12 (0.01)	1.15 (0.01)	2.59 (0.035)	Neat	170	15–20	*S*-**1**	48.8	54
3	**4**	6.3 (0.05)	5.75 (0.05)	3.5 (0.05)	DMSO	180	rt	*S*-**2**	63[c]	68
4	**4**	1.26 (0.01)	1.15 (0.01)	2.5 (0.035)	Neat	50	rt	*S*-**2**	43.8	45
5	**4**	1.26 (0.01)	0.575 (0.005)	2.1 (0.03)	Neat	180[d]	rt	*S*-**2**	42.0	38
6	**10**	2.8 (0.025)	2.1 (0.03)	4.56 (0.03)	Neat	82	rt	*S*-**14**[e]	27.2[f]	48
7	**11**	5.0 (0.039)	2.8 (0.04)	2.87 (0.025)	Neat	82	rt	*R*-**7**[e]	33.8[g]	49
8	**12**	1.40 (0.01)	1.05 (0.015)	1.15 (0.01)	Neat	70	rt	*S*-**15**[e]	9.3[f]	47
9	**13**	2.10 (0.01)	0.875 (0.0125)	1.15 (0.01)	Neat	72	rt	±**16**	0	43

[a] Recrystallized *S*-proline $[\alpha]_D^{25} = -82$ (*c* 4.4, H_2O) was used.

[b] The ee for *S*-**1** and *S*-**2** based on reported values for 100% pure enantiomers *S*-**1** $[\alpha]_D^{25} = +367$ (*c*, 1, C_6H_6), *S*-**2** $[\alpha]_D^{25} = +100$ (*c* 1.4, C_6H_6).

[c] 100% *S*-**1** and *S*-**2** can be obtained from these products by cooling and recrystallizing twice from ether–hexane.

[d] UV absorption (242 nm) reached a maximum value after about 60 h.

[e] $[\alpha]_D^{25}$ for *S*-**14**, *R*-**7** and *S*-**15** were +4.4 (*c* 2.9, CH_3OH), −2.6 (*c* 0.08, $CHCl_3$) and +3.1 (*c* 2, CH_3OH), respectively.

[f] The ee was determined by chiral HPLC analysis using a Chiralcel OJ column.

[g] The ee was determined by ^1H NMR analysis of Mosher esters of the carbinols obtained by $NaBH_4$ reduction of the unconjugated carbonyl group.

formation of the spiroenediones probably involves, as in the case of *S*-**2**, the formation of a Michael adduct followed by a kinetically controlled cyclization in the presence of *S*-proline. In the case of 2-formylcyclohexanone **11**, one-pot annulation gives the *R*-product in contrast to **10** and **12**, which give *S*-products. This difference may stem from the preferred geometries (*Z* or *E*) of the hydrogen-bonded complexes of *S*-proline with 2-hydroxymethylenecycloalkanones. The anomalous result in the case of (±)-**16** is probably due to the more flexible geometry of the 12-membered ring, leveling the energy difference between the *Z* and *E* geometries of the complex involved.

4. General procedure for one-step 'neat' syntheses of spiroenediones (*S*-14, *R*-7 and *S*-15)

A mixture of finely ground proline (0.01 mol) and 2-formylcycloalkanone (0.01 mol) was stirred at room temperature for 2 h under a nitrogen atmosphere. Freshly distilled MVK (0.012 mol) was then added dropwise over a 30 min period. Stirring was continued for an additional period (see Table 1). The resultant brown viscous mass was stirred with CH_2Cl_2 (150 ml) and the organic extract was washed with water (2×50 ml), brine, then dried and the solvent was removed. The residue was purified by flash-column chromatography (silica gel) using chloroform as eluant.

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