

Enantioselective solvent-free Robinson annulation reactions

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Abstract. The enantioselective cyclization of the prochiral cyclic substrates **1** to **7** and **26**, can be carried out in the *neat* using *S*-proline as catalyst. The substrates **18** to **22** and **27** could not be cyclized with *S*-proline but could be cyclized with a mixture of *S*-phenylalanine and *d*-camphorsulphonic acid. The enantioselective cyclization of prochiral acyclic triones **45** and **47** and also the racemic tricarbonyl compounds **54** to **57** could also be carried out in the *neat* using *S*-proline as catalyst. The optically active enediones obtained in the above cyclizations could also be obtained directly from 1,3-diones or 2-hydroxymethylene cycloalkanones in a one-pot reaction with methyl vinyl ketone (MVK) and *S*-proline in the absence of solvents. ¹³C NMR studies of the one-pot synthesis of **S-11** and **S-14** reveal that the annulations involve initial formation of an acid-base complex followed by a Michael reaction and then an enantioselective cyclization. Such enantioselective cyclizations probably occur on the surface of *S*-proline crystals.

Keywords. Enantioselective annulation; cyclization; *S*-proline; *S*-phenylalanine; *d*-camphorsulphonic acid.

1. Introduction

Robinson annulation reactions have a distinct place in synthetic organic chemistry because of their ability to provide a four-carbon chain in a single step leading to annulated carbocyclic molecules¹. The use of proline or any other amino acid in asymmetric annulation reactions in a solid–liquid phase reaction in the absence of solvents to effect an asymmetric synthesis is an important step forward towards cleaner synthesis². Environmental and economic pressures are now forcing the chemical community to search for more efficient ways of performing chemical transformations. With asymmetric synthesis so much to the fore in current thinking, it is important to seek chiral transfer reactions that can operate *neat*.

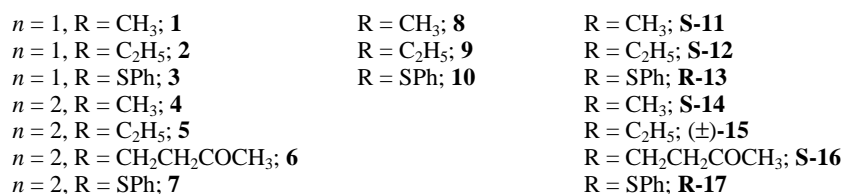
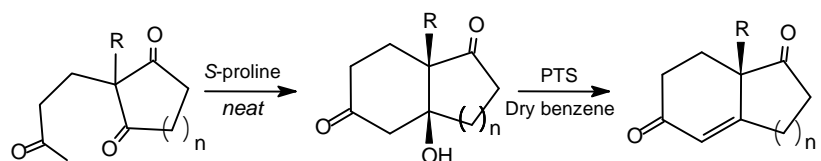
Reports on solvent-free reactions have become increasingly frequent and the field has developed into an important branch of ‘Green chemistry’³. Such solvent-free reactions include reactions between solids⁴, between gases and solids and non-supporting inorganic reagents. In continuation of our preliminary communication², we wish to present more comprehensively here our results on enantioselective Robinson annulation

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reactions. The diketones **S-11** and **S-14** are potential chiral synthons for the synthesis of steroids, terpenes and natural products^{5,6}. These diketones can be obtained by asymmetric cyclization using *S*-proline, as reported² by us in the absence of solvents of prochiral triones **1** and **4** respectively. With a view to extend the scope of such solvent-free reactions, we have studied the enantioselective cyclization of three different types of substrates viz.,

(i) prochiral cyclic, (ii) prochiral acyclic and (iii) racemic substrates.



Scheme 1. Cyclization using *S*-proline as a chiral auxiliary.

Table 1. Cyclizations using *S*-proline.

Substrate	Wt. (g) of substrate (mol)	Proline <i>S/R</i>	Wt. (g) of proline (mol)	Time (h)	Temp. (°C)	Product	$[\alpha]_D^{25}$	<i>e/e</i> (%)	Yield (%)
1	1.82 (0.01)	<i>S</i>	0.055 (0.0005)	88	15–20	S-11	+ 220.86°	60.2	66
1	1.82 (0.01)	<i>R</i>	0.055 (0.0005)	82	25	R-11	– 272.68°	74.3	59
2	1.96 (0.01)	<i>S</i>	0.055 (0.0005)	100	22–25	S-12	+ 204.36°	78	68
3	1.0 (0.0038)	<i>S</i>	0.02 (0.00019)	150	18–20	R-13	+ 74°	64.7	33
4	0.98 (0.005)	<i>S</i>	0.03 (0.00035)	68	RT	S-14	+ 64.7°	64.7	33
4	1.96 (0.01)	<i>R</i>	0.0575 (0.0005)	70	RT	R-14	– 67.1°	67.1	32
5	2.10 (0.01)	<i>S</i>	0.0575 (0.0005)	90	RT	(±)- 15	0	0	52
6	2.52 (0.01)	<i>S</i>	0.0575 (0.0005)	65	RT	S-16	+ 26.2°	*	48
7	0.800 (0.0029)	<i>S</i>	0.016 (0.00014)	140	20	R-17	– 97.5°	50	34

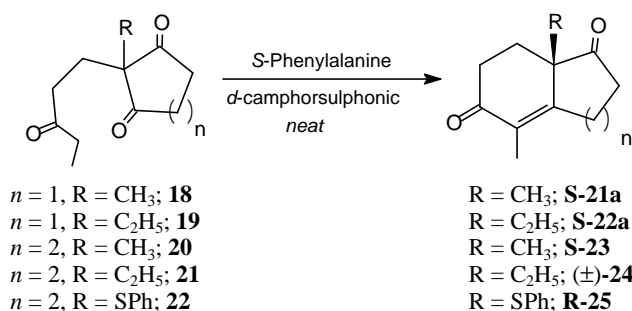
**e/e* not determined

2. Cyclization

2.1 Cyclization of prochiral cyclic substrates

The prochiral triketones (scheme 1) were prepared according to the literature method⁷. The cyclizations were carried out under nitrogen atmosphere in the *neat*². Table 1 gives optimum conditions to get the various products in maximum chemical as well as optical yields. The products were characterized by IR, NMR and mass spectra. Enantiomeric excess of the product was calculated on the basis the know specific rotations of the enantiomerically pure compounds. In the case of cyclopentane derivatives, the initial products were ketols which were dehydrated by refluxing with PTS in dry benzene.

The *neat* asymmetric cyclization could be extended to other prochiral cyclic triones (**18–22**) obtained using ethyl vinyl ketones a Michael acceptor (scheme 2). Our attempts to cyclize these triketones using *S*-proline were unsuccessful; however a mixture of *S*-phenylalanine and *d*-camphorsulphonic acid (1:1) was found to effect cyclization in the absence of solvent. The products obtained were characterized by IR and NMR, and *e/e* was calculated for known compounds on the basis of specific rotations reported in the literature. Table 2 gives the optimum conditions for the various cyclizations.



Scheme 2. Cyclization using *S*-phenylalanine and *d*-camphorsulphonic acid mixture.

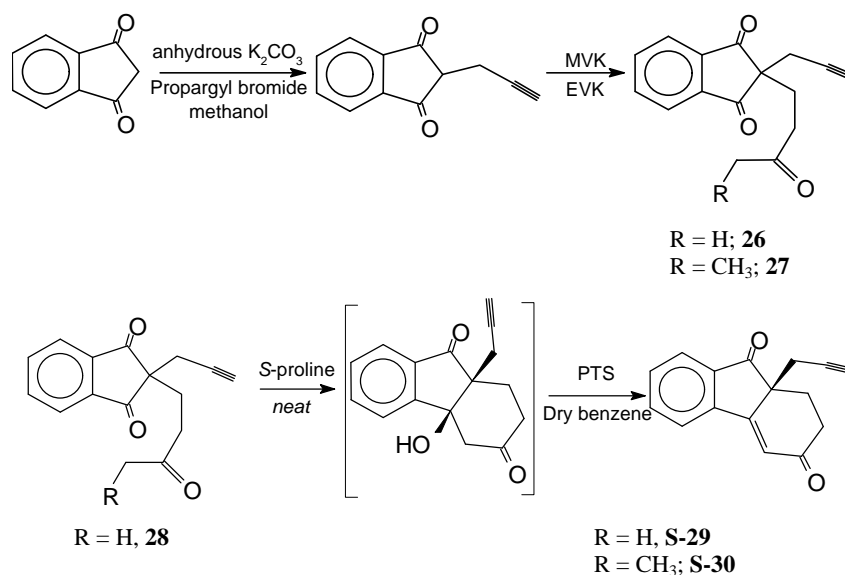
Table 2. Cyclizations using *S*-phenylalanine and *d*-camphorsulphonic acid mixture.

Substrate	Wt. (g) of substrate (mol)	Wt. (g) of <i>S</i> -phenylalanine (mol)	Wt. (g) of <i>d</i> -camphorsulphonic acid (mol)	Time (h)	Temp. (°C)	Product	$[\alpha]_D^{25}$	<i>e/e</i> (%)	Yield (%)
18	1.96 (0.01)	1.65 (0.01)	1.16 (0.005)	24	80	S-21a	+ 266.2°	79	59
19	1.0 (0.005)	0.850 (0.005)	0.550 (0.0025)	20	73	S-22a	+ 189°	*	55
20	2.13 (0.01)	1.65 (0.01)	1.16 (0.005)	30	72–75	S-23	+ 114°	82	53
21	0.550 (0.0025)	0.400 (0.0025)	0.280 (0.00025)	25	75	(±)- 24	0	–	61
22	3.0 (0.01)	1.65 (0.01)	1.16 (0.005)	22	90	R-25	+ 33°	*	48

**e/e* not determined

The yields in the above *neat* cyclization using *S*-phenylalanine and *d*-camphor-sulphonic acid are comparable with those obtained⁸ in solvent in at least one case, **S-23**.

In continuation, we have successfully carried out the *neat* cyclization of triones of the type **26** and **27** obtained from indane 1,3-dione as depicted in scheme 3.



Scheme 3. Cyclization of derivatives of indane-1,3-dione.

Table 3. Cyclization of trione-2,6.

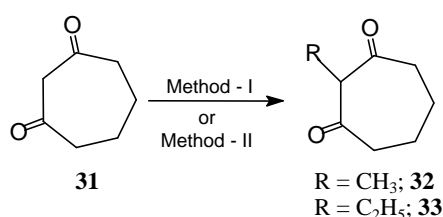
Substrate	Wt. (g) of substrate (mol)	Proline S/R	Wt.(g) of proline (mol)	Time (h)	Temp. (°C)	Product	[α] ²⁵ _D	Yield (%)
26	0.500 (0.002)	<i>S</i>	0.040 (0.00034)	58	RT	S-29	+ 112°	58
26	0.500 (0.002)	<i>R</i>	0.230 (0.002)	60	RT	R-29	- 112.1°	62

The compound **S-29** has been used for the synthesis of the Gibbane framework by Takano *et al*⁹. The literature method of preparation of **S-29** involves cyclization of propargyl trione **26**, using *S*-proline as chiral auxiliary in *N,N*-dimethylformamide. The same cyclization could be carried out using *S*-proline in the *neat* under nitrogen atmosphere. The results are summarized in table 3. The reaction was also performed using pyrrolidine/acetic acid in dry ether at lower temperature. The racemic diketone (\pm)-**29** was characterized by IR, NMR and mass spectra and further confirmed by X-ray analysis¹⁰.

Our attempts to cyclize the trione **27** using proline were unsuccessful. Instead a combination of *S*-phenylalanine and *d*-camphorsulphonic acid was found to be effective in bringing about cyclization of trione **27** to **S-30**. The compound **S-30** was characterized by IR, NMR and mass spectral data.

The cyclization of triones obtained from cyclopentane and cyclohexane 1,3-diones has prompted us to investigate the triones derived from cycloheptane 1,3-dione¹¹ (scheme 4).

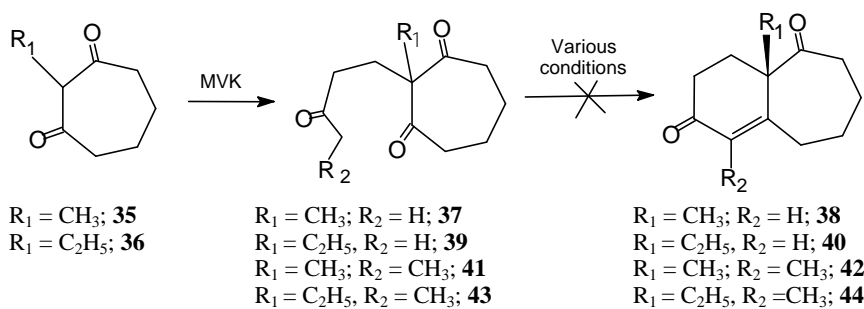
This dione was treated with methyl/ethyl iodide in the presence of potassium *t*-butoxide in *t*-butanol or alternatively with DBU/anhydrous LiI and alkali iodide in dry THF maintained at 65–70°C. The 2-alkyl cycloheptane-1,3-diones were obtained in 92–95% yield (based on recovered starting dione).



Method I: Potassium *t*-butoxide/*t*-butanol/CH₃ or C₂H₅ at 60–65°C

Method II: DBU–anhydrous LiI/CH₃ or C₂H₅ in dry THF at 60°C.

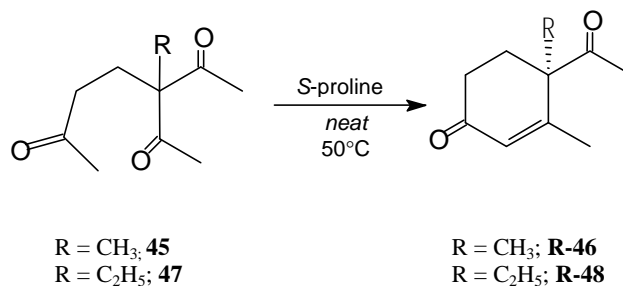
Our attempts to cyclize triones **37**, **39**, **41** and **43** (scheme 4) using either proline or a combination of *S*-phenylalanine and *d*-camphorsulphonic acid did not yield the expected optical-active products either in solvent or under *neat* condition. Surprisingly, however, cyclization of the same trione could be done using pyrrolidine/acetic acid in dry ether to give the corresponding *dl* products **38**, **40**, **42** and **44** in 60–65% chemical yield. The structures were confirmed by IR, NMR and mass spectra. The structure of trione **39** and diketone (\pm)-**40** were further confirmed by X-analysis¹².



Scheme 4. Attempted asymmetric cyclizations of cycloheptane-1,3-dione derivatives.

2.2 Cyclization of prochiral acyclic substrates

Next, it was of interest to study the *neat* cyclization of some prochiral acyclic substrates (scheme 5). 3-Acetyl-3-methyl-2,6-heptane-dione (**45**) and 3-acetyl-ethyl-2,6-heptane-dione (**47**) were easily obtained by literature methods as liquids. These triones on



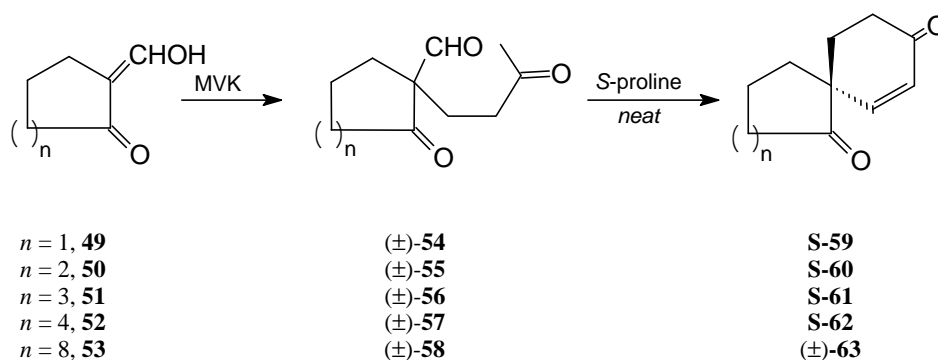
Scheme 5. Cyclizations of triones **45** and **47**.

treatment with *S*-proline under nitrogen atmosphere at 50–55°C gave the cyclized products **R-46** and **R-48** respectively. IR and NMR data confirmed the structures; the stereochemistry of **R-46** was deduced by comparison of rotation with the product obtained earlier using solvent. The configuration of **R-48** is assumed by analogy to **R-46**.

The reaction conditions used are tabulated in table 4. As far as the above acyclic substrates are concerned, the *neat* technique seems inferior to the reported solvent-mediated cyclization¹³.

2.3 Cyclization of racemic substrates

In further studies of our *neat* techniques, attention was focussed on *S*-proline mediated cyclization of racemic tricarbonyl compounds of type **54** (scheme 6). These cyclizations must involve kinetic resolution; one of the two possible diastereoisomers with *S*-proline must be reacting faster than the other. The required starting materials namely 2-hydroxymethylene cycloalkanones and its Michael adducts were prepared according to literature procedures¹⁴.



Scheme 6. Asymmetric cyclizations of racemic triones.

Table 4. Cyclisation of triones **45** and **47**.

Substrate	Wt. (g) of substrate (mol)	Proline S/R	Wt. (g) of proline (mol)	Time (h)	Temp. (°C)	Product	$[\alpha]_D^{25}$	<i>e/e</i> (%)	Yield (%)
45	184 (0.01)	<i>S</i>	1.15 (0.01)	50	50	R-46	+20.2°	12	42
45	1.84 (0.01)	<i>R</i>	0.060 (0.0005)	55	60	S-29	-5.3°	3.1	43
47	1.98 (0.01)	<i>S</i>	1.15 (0.01)	52	52	R-48	+9°	*	45

e/e* not determinedTable 5.** Asymmetric cyclization of racemic triones.

Substrate	Wt. of (g) substrate (mol)	Proline S/R	Wt. of (g) proline (mol)	Time (h)	Temp (°C)	Product	$[\alpha]_D^{25}$	<i>e/e</i> (%)	Yield (%)
54	1.82 (0.01)	<i>S</i>	0.057 (0.005)	90	RT	S-59	+4.8°	29	47
54	2.8 (0.015)	<i>R</i>	0.090 (0.0007)	68	RT	R-59	-4.62°	28	39
55	4.0 (0.02)	<i>S</i>	0.120 (0.001)	40	RT	S-60	+3.19°	39.8	58
56	4.2 (0.02)	<i>S</i>	0.115 (0.001)	136	RT	S-61	+1.17°	3.5	55
56	3.5 (0.016)	<i>R</i>	0.095 (0.00083)	72	RT	S-61	-4.17°	12.3	53
57	2.62 (0.0117)	<i>S</i>	0.067 (0.00058)	72	RT	S-62	+31.2°	*	52
58	4.2 (0.015)	<i>S</i>	0.230 (0.002)	140	RT	(±)- 63	0	0	92

**e/e* not determined

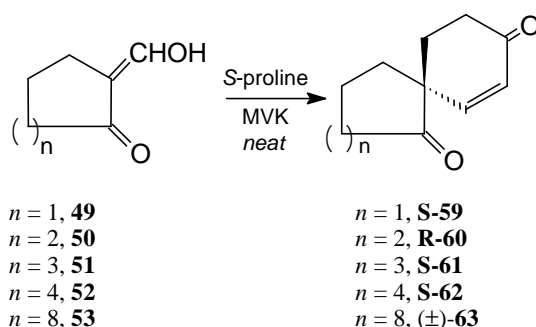
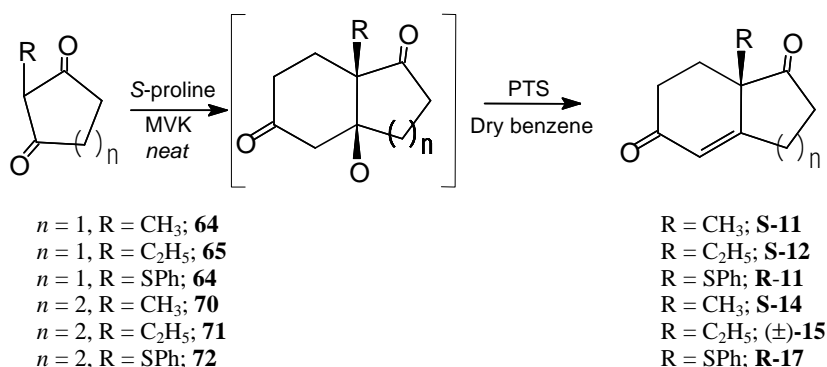
The cyclization of the Michael adducts (±)-**54**–(±)-**58** was carried out by stirring with *S*-proline in the *neat* at room temperature under nitrogen atmosphere. The results of different experiments are summarized in table 5.

The tricarbonyl compound (±)-**58**-cyclododecanone derivative is a solid with mp. 89–90°C. It was of particular interest to attempt its *neat* asymmetric cyclization with *S*-proline – another solid; if successful, it would be the first example of chiral transfer in the solid state using a chiral auxiliary. The *neat* experiment was repeated a number of times with care taken to ensure thorough mixing of the two reactants using small glass beads. The product isolated turned out to be (±)-**63** in addition to recovered tricarbonyl compound and it was identical in all respects to the authentic sample prepared by NaOEt catalyzed cyclization of (±)-**58**. The anomalous behaviour of the tricarbonyl compound (±)-**58** is probably due to the more flexible geometry of the 12-membered ring, levelling the energy difference between the diastereoisomers with proline and leading to equal rates of cyclization.

3. One-pot synthesis of optically active Wieland–Miescher ketones and similar enones in the *neat*

Earlier we reported¹⁵ that either of the enantiomers **S-60** or **R-60** can be obtained from formylcyclohexanone by one-step and two-step processes using the *same chiral auxiliary*. The enantioselectivity was reversed in the above reaction when *R*-proline was used instead of *S*-proline. It was tempting therefore to extend the above one-step methodology to the synthesis of **R-11** using *S*-proline itself since such a process, if successful, will be less expensive than the literature procedure. This expectation did not materialize; instead a convenient one-pot synthesis of **S-11** resulted, in contrast to the literature procedure.

This procedure involves a two-step process in which the Michael adduct is prepared first and then cyclodehydrated. In the one-pot procedure, dione **64** and *S*-proline are stirred together for 30 min at 15–20°C followed by the addition of methylvinylketone (MVK) under nitrogen atmosphere. The stirring is continued for several hours (table 6). The reaction could be carried out both in solvent medium as well as in the *neat*. After the stated period, the crude ketone without further purification, was dehydrated by treatment with PTS in dry benzene. After usual work up and purification, pure diketone **S-11** was obtained. The enantiomeric excess was calculated on the basis of the specific rotation of 100% pure enantiomer⁷. The one-pot synthesis was extended to the cyclization of other



Scheme 7. One-pot synthesis of chiral enones.

Table 6. One-pot synthesis of chiral enones.

Substrate	Wt. (g) of substrate (mol)	Wt. (g) of MVK (mol)	Proline S/R	Wt. (g) of proline (mol)	Time (h)	Temp. (°C)	Product	<i>e/e</i> (%)	Yield (%)
49	2.8 (0.025)	2.1 (0.03)	<i>S</i>	2.87 (0.025)	82	RT	S-59	27.2	48
50	5.0 (0.039)	2.8 (0.04)	<i>S</i>	4.56 (0.039)	82	RT	R-60	33.8	49
51	1.40 (0.01)	1.05 (0.015)	<i>S</i>	1.15 (0.01)	70	RT	S-61	9.3	47
52	4.0 (0.025)	2.1 (0.030)	<i>S</i>	2.875 (0.025)	70	RT	S-62	(*)	52 ^a
53	2.10 (0.01)	0.875 (0.0125)	<i>S</i>	0.0575 (0.0005)	110	RT	(±)- 63	0	63
64	1.12 (0.01)	2.5 (0.035)	<i>S</i>	1.15 (0.01)	170	15–20	S-11	48.8	24
65	1.26 (0.01)	1.2 (0.017)	<i>S</i>	1.15 (0.01)	100	12–20	S-12	65.5	34
66	1.26 (0.01)	2.5 (0.035)	<i>S</i>	1.15 (0.01)	50	RT	S-14	43.8	25
71	1.28 (0.01)	1.4 (0.02)	<i>S</i>	1.15 (0.01)	105	RT	(±)- 15	0	58 ^b
72	0.440 (0.01)	0.210 (0.03)	<i>S</i>	2.30 (0.02)	140	20–25	R-17	7	22

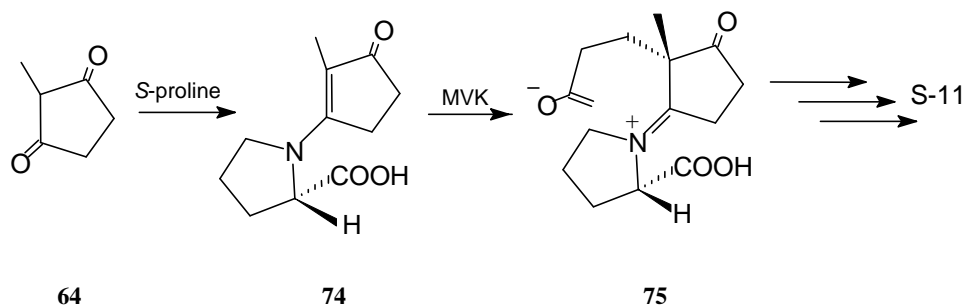
**e/e* not determined; ^areaction was carried out in DMSO; ^battempts to get optically active form in both one-step and two step processes failed

prochiral and racemic substrates (scheme 7). The results are summarized in table 6. In general, using one-step procedure, products whenever solid could be obtained in 90% *e/e* by repeated recrystallization; however the overall chemical yield was always less when compared with yield in two-step process. Also one major drawback of the one-step process was the need to use the chiral auxiliary in equivalent molar amount.

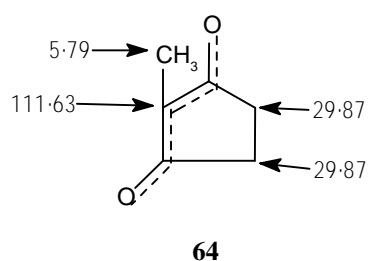
3.1 Mechanism of the one-pot process

Two mechanisms may be considered for the above one-pot formation of **S-11**, **S-14** and other related compounds. Taking the case of **S-11**, its formation may involve preferential formation of chiral enamine **74** from the reaction of *S*-proline with pro-*R* carbonyl group of dione **64** followed by Michael addition on the *Si* face with MVK to yield *S*-enamine **74** and *S*-enamonium **75** intermediates (scheme 8). The intermediate **75** can be visualized as getting transformed to **S-11** by more than one pathway.

It was of interest to determine if NMR evidence for the intermediates **74** or **75** could be obtained. Equivalent amounts of 2-methyl-1,3-cyclopentane dione **64** and *S*-proline were mixed together in DMSO-*d*₆, and allowed to stand for 3–4 h. Distilled methyl vinyl ketone (1 equiv.) was the added. ¹³C NMR revealed that the initially insoluble proline forms a soluble complex with the 2-methyl-1,3-cyclopentane dione **64** and then reacts with MVK. Immediately after the addition of MVK, signals are seen for trione **1**, ketol **8**, the soluble proline–dione complex **67** and unreacted MVK. After 3 h, the formation of ketol **8** is complete with no trace of MVK, trione **1** or the proline complex. Continued



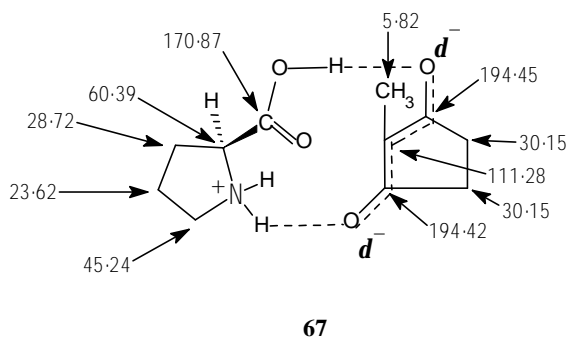
Scheme 8. Mechanism of the one-pot process.



standing (up to 68 h) shows mainly ketol **8** with trace of enone **S-11**. There was no evidence for the formation of enamine intermediate **74** or enammonium intermediate **75**.

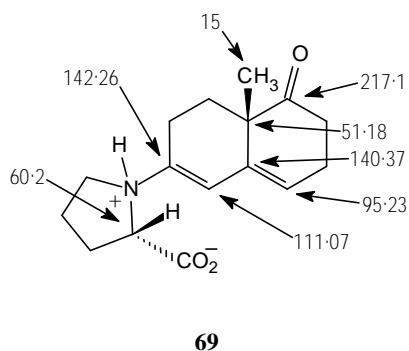
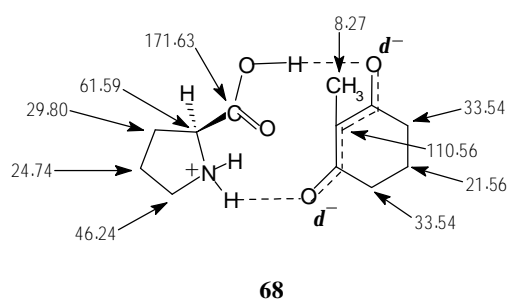
Evidently, the soluble proline complex **67** gives Michael adduct **1** directly *in situ*; this adduct then cyclized to ketol **8**.

The proline complex with 2-methyl-1,3-cyclopentane dione **67** in $\text{DMSO-}d_6$ has the ^{13}C signals indicated.



The one-step with 2-methyl-1,3-cyclohexane dione **70** was similarly monitored by taking ^{13}C NMR spectra at regular intervals over a period of 22 h. 2-Methyl-1,3-cyclohexane dione **70** (0.25 mmol), in 0.5 mL of $\text{DMSO-}d_6$ showed carbon signals at δ 7.26, 21.59, 33.54 and 109.66. The absence of ketone carbonyl revealed that the 1,3-dione **70** mostly exists in enol form. On adding *S*-proline to the dione **70**, it forms a soluble proline-1,3-dione complex whose carbon signals are shown in the structure **68**.

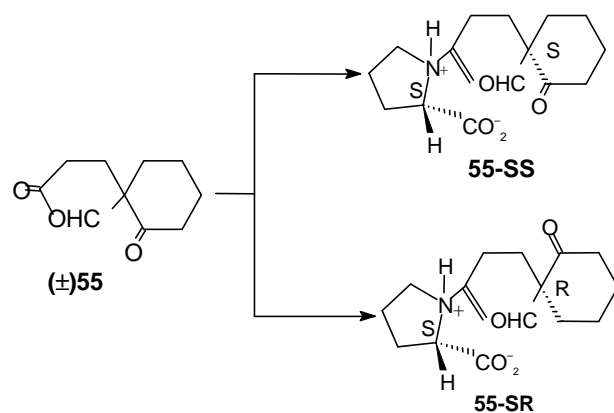
Even after 5 h, there was no change in the spectrum of the mixture indicating the formation of a stable complex between dione **70** and *S*-proline. Such a complex **68** automatically ruled out the formation of any enamine derivative. Distilled MVK (0.25 mmol) was added to the above mixture and the reaction was monitored by taking ^{13}C NMR spectrum at intervals of 15 min in the initial stages of reaction and later on every two hours towards the end of the reaction. Immediately after the addition of MVK, carbon signals are seen for trione **4**, strong signals for the proline-1,3-dione complex **68** and MVK. After 3.5 h, enedione **S-14** starts showing up weak signals at δ 124.96 and 166. After 22 h, one observes signals for diketones **S-14** along with very weak signals for dienamine **69** and MVK. Evidently the trione **4** is the primary product formed *in situ*, undergoing cyclization as described earlier.



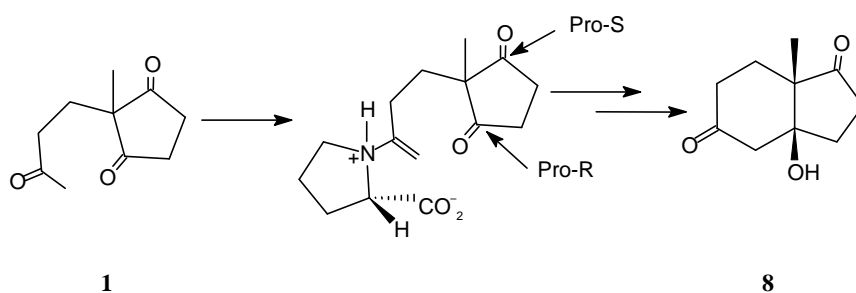
The above mechanism, though demonstrated for the one-step process carried out in DMSO, is probably also followed in the reaction carried out without solvent, since *S*-proline is practically insoluble in anhydrous DMSO.

4. Mechanism of enantioselective annulation

The enantioselective cyclization of both prochiral triones and racemic tricarbonyl compounds to optically active enediones must involve kinetic resolution. On the basis of the currently accepted enamine mechanism, one of the distereoisomeric enamine intermediates may cyclize faster than the other leading to an excess of one enantiomer. For example, enamine **55-SR** may be more reactive than **55-SS** and cyclize faster to give an excess of enantiomeric product.



In the case of prochiral triketones like **1**, the chiral enamines intermediate may be reacting faster with the pro-*R* carbonyl of the ring – leading to excess of ketol, **8**.



However, spectroscopic evidence has been obtained which rules out the enamine mechanism for the above type of asymmetric cyclization. Instead, a template mechanism¹⁶ involving protonation and deprotonation of the triketone **1** on the surface of *S*-proline crystal has been proposed. The hydrogen-bonded complexes of *S*-proline with pro-*S* and pro-*R* carbonyl groups of **1** may differ in energy and reactivity leading to chiral discrimination.

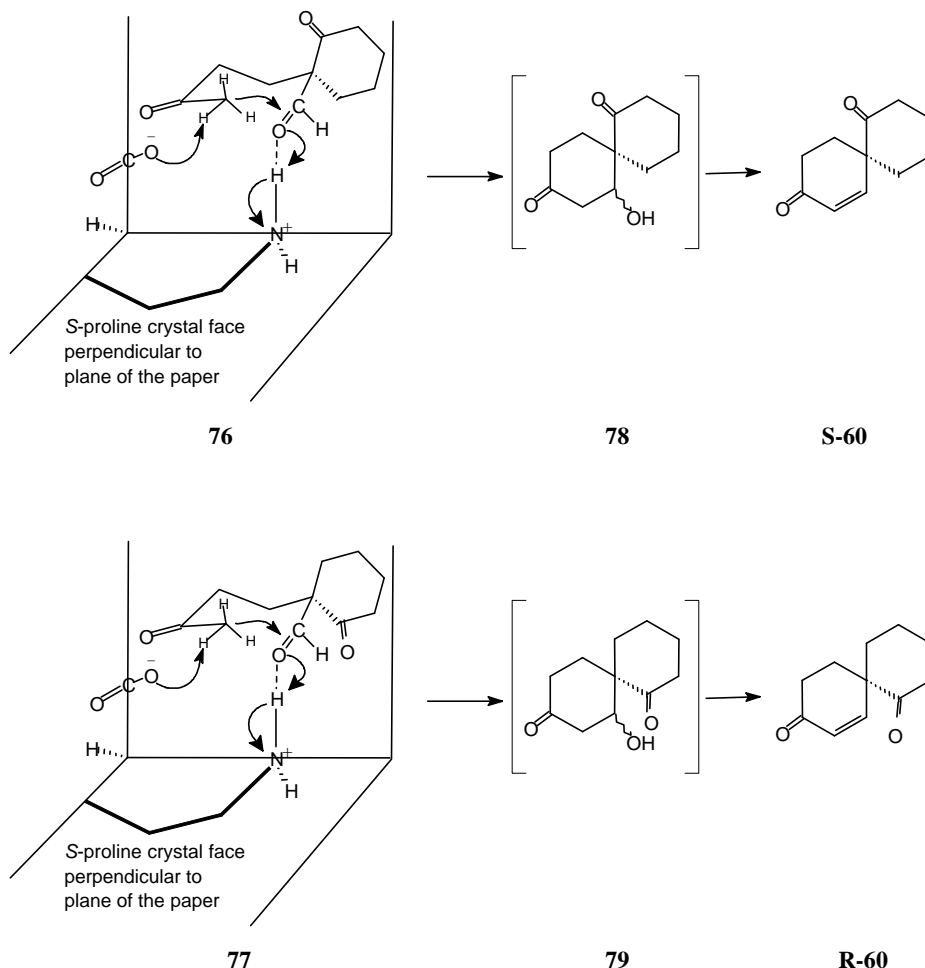
Similarly with $(\pm)55$, *S*-proline can form diastereoisomeric hydrogen-bonded complexes **76** and **77**. They differ in energy and reactivity and hence may lead to enantioselective cyclization of $(\pm)55$.

In summary, asymmetric synthesis of a series of annulated carbocycles using suitable chiral auxiliary in the absence of solvent has been achieved.

5. Experimental

5.1 General considerations

All melting point and boiling points are uncorrected. IR spectra were recorded on a Shimadzu FTIR 230. ¹H and ¹³C NMR spectra were recorded in CDCl₃ using TMS as an internal standard on a Jeol GX 400 spectrometer at 400 MHz and 100.4 MHz



respectively. Mass spectra were recorded on a Finnigan MAT-8230 GC mass spectrometer. Enantiomeric excess of compounds **S-59** and **S-61** were determined using Chiralcel OJ/chiralcel AD chiral column using *n*-hexane/IPA (100:1) as an eluant with flow rate of 1.0 mL/min. Analytical data are given for unknown compounds only.

5.2 General procedure for reactions carried out in the absence of solvent – two-step synthesis using proline

In a dried round-bottomed flask, the Michael adduct was mixed with dried and powdered proline and allowed to stir under nitrogen atmosphere at room temperature. The progress of the reaction was monitored by following UV absorption of the characteristic of the product, whenever possible or after dehydration of ketol. After completion of the reaction, the entire reaction mixture was extracted with methylene chloride and the extract was washed (twice) with water to remove unreacted *S*-proline, dried

over anhydrous MgSO_4 and solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography using 25% ethyl acetate:hexane as eluant.

5.3 *General procedure for reactions carried out in the absence of solvent via two-step process using S-phenylalanine and d-camphorsulphonic acid*

In an oven-dried round-bottomed flask, a mixture of Michael adduct (0.01 mmol), *S*-phenylalanine (0.01 mmol) and *d*-camphorsulphonic acid (0.005 mmol) was stirred in the absence of solvent at room temperature under nitrogen atmosphere for 24 h. The mixture was heated initially at 40°C for 5 h then at 60°C for 12 h, and finally at 74°C for 5 h. The resulting viscous mass was powdered into cold aqueous NaHCO_3 and extracted with methylene chloride (100 mL). Evaporation of solvent under reduced pressure followed by column chromatographic purification of the crude residue afforded the cyclized product.

5.4 *General procedure for one-step neat synthesis*

A 100 mL three-necked round-bottomed flask was charged with finely ground proline (0.01 mol) and 2-alkyl-1,3-dione (0.01 mol), and mixed well for 1 h at room temperature under nitrogen atmosphere. Methyl vinyl ketone (0.015 mol) was then added dropwise over 0.5 h. The reaction mixture was stirred for an additional period and completion of reaction was monitored by taking UV spectrum in absolute ethanol. The resultant brown coloured viscous mass was then extracted with methylene chloride (2×100 mL) and the extract thoroughly washed with distilled water (2×50 mL). The organic layer was washed with brine and dried over anhydrous MgSO_4 . The solution was filtered and the filtrate concentrated under reduced pressure. The residue was chromatographed on flash silica gel using chloroform as eluant.

5.5 *General procedure for one-step neat synthesis from 2-hydroxymethylene cycloalkanones using proline*

A 100 mL three-necked round bottom flask containing magnetic stirrer was charged with (0.01 mol) of finely ground proline and 2-hydroxymethylene cycloalkanones (0.01 mol) and stirred at room temperature under nitrogen atmosphere for 2 h. Freshly distilled methyl vinyl ketone (0.012 mol) was added drop wise to the above mixture over 0.5 h. Stirring was continued for an additional period and completion of reaction was monitored by taking UV spectrum in absolute ethanol. The resultant brown coloured viscous mass was treated with methylene chloride (150 mL) and organic extract was washed with water (2×50 mL) and brine, dried and the solvent removed under reduced pressure. The residue was purified by flash column chromatography using chloroform as eluant.

5.6 (+)-(8a-S)-(3-oxobutyl)-3,4,8,8a-tetrahydro-1,5 (2H, 7H)-naphthalenedione, **S-16**

Following the general procedure, compound **S-16** was obtained as liquid by cyclization of tetraketone **6** in the absence of solvent. Yield: 48–55%; IR (CHCl_3), cm^{-1} : 1717, 1705 (saturated carbonyls); 1675 (conjugated carbonyl); 1605 (olefinic bond); $^1\text{H NMR}$ **d** 5.78

(s, 1H, vinylic proton); 2.18 (s, 3H, $-\text{COCH}_3$), 1.51–2.82 (m, 14H, methylene protons), ^{13}C NMR **d** 210.66, 209.13, 197.92, 165.71, 125.45, 50.34, 37.35, 36.50, 33.32, 31.46, 29.44, 29.08, 22.96, 22.66; $[\alpha]_{\text{D}}^{25}$: +26.2° (C, 3.5, benzene); MS (*m/z*): 234 (M^+); CD (nm): (q_{obs})₃₆₅ = -5×10^{-3} deg (C = 0.005, dioxane), (q_{obs})₃₂₂ = $+48 \times 10^{-3}$ deg (C = 0.005, dioxane), (q_{obs})₂₉₄ = $+77 \times 10^{-3}$ deg (C = 0.005, dioxane); Analysis: $\text{C}_{14}\text{H}_{18}\text{O}_3$ requires C = 71.77, H = 7.74%; Found: C = 71.71, H = 7.69%.

5.7 (+)-(8*aR*)-3,4,8,8*a*-tetrahydro-8*a*-thiophenyl-5-methyl 1,6-(2*H*, 7*H*) naphthalene-dione, **R-25**

Following the general procedure the compound **R-25** was obtained by asymmetric cyclization of prochiral trione **22**. Yield: 41%; m.p.: 106–108°C; IR (KBr), cm^{-1} : 1703, 1665; ^1H NMR **d** 7.20–7.25, 2.03–3.11 (m, 10H, methylene proton), 1.75 (s, 1H, vinylic methyl); ^{13}C NMR **d** 211.33, 196.98, 157.52, 130.64, 50.11, 36.78, 32.67, 29.10, 26.24, 22.80, 10.39, 129.29, 128.94, 125.47, 123.72; $[\alpha]_{\text{D}}^{25}$: +33° (C, 2, chloroform); MS (*m/z*): 286 (M^+); CD (nm): (q_{obs})₂₄₃ = -2.15×10^{-3} deg (C = 0.005, dioxane); Analysis: $\text{C}_{17}\text{H}_{18}\text{O}_2\text{S}$ requires C = 71.28, H = 6.33%, Found: C = 71.34, H = 6.28%.

5.8 (+)-(9*aS*)-propargyl-4-methyl-1,2,3,9-tetrahydrofluorene-3,9-dione, **S-30**

Following the general procedure the compound **S-30** was obtained by asymmetric cyclization of prochiral trione **27**. Yield: 56%; m.p.: 131–133°C; IR (KBr), cm^{-1} : 1725 (saturated carbonyl), 1682 (conjugated carbonyl); 1602 (olefinic bond). ^1H NMR **d** 7.52–7.94 (m, 4H, aromatic protons), 2.62 (d, $J = 2$ Hz, $-\text{CH}_2-\text{C}\equiv\text{CH}$); 2.12–2.60 (m, 4H, methylene protons); 1.92 (t, $J = 2$ Hz, 1H, $\text{HC}\equiv\text{C}-\text{CH}_2$); 1.82 (s, 3H, vinylic methyl); ^{13}C NMR **d** 201.59, 197.95, 159.56, 144.97, 136.17, 135.60, 132.53, 124.50, 122.96, 119.44, 78.18, 73.31, 50.27, 33.37, 26.11, 25.74, 20.36; $[\alpha]_{\text{D}}^{25}$: +33° (C, 3.1, chloroform); MS (*m/z*): 250 (M^+); CD (nm): (q_{obs})₂₈₅ = $+3.3 \times 10^{-3}$ deg (C = 0.009, dioxane) (q_{obs})₃₄₀ = -0.140×10^{-3} deg (C = 0.009, dioxane); Analysis: $\text{C}_{17}\text{H}_{14}\text{O}_2$ requires C = 81.58, H = 5.63%, Found: C = 81.56, H = 5.66%.

5.9 (+)-(7*aS*)-1,5-dioxo-methyl-7*a*-ethyl-2,3,5,6,7*a*, hexahydroindene **S-22a**

Following general procedure, the compound **S-22a** was obtained as a liquid from prochiral trione **19** in solvent-free condition. Yield: 55%; IR (CHCl_3), cm^{-1} : 1739 (saturated carbonyls); 1670 (conjugated carbonyl); 1608 (olefinic bond); ^1H NMR **d** 1.91–2.92 (m, 10H methylene protons); 1.82 (s, 3H, vinylic methyl); 0.99 (t, 3H, $-\text{CH}_2\text{CH}_3$); ^{13}C NMR **d** 216.44, 197.44, 162.78, 129.49, 52.29, 35.17, 32.11, 27.21, 24.86, 24.38, 10.35, 8.60; $[\alpha]_{\text{D}}^{25}$: +189° (C, 1.4, benzene); MS (*m/z*): 192 (M^+); CD (nm): (q_{obs})₂₉₄ = $+2.1 \times 10^{-3}$ deg (C = 0.006, dioxane), (q_{obs})₂₄₅ = -2.4×10^{-3} deg (C = 0.006, dioxane); Analysis: $\text{C}_{12}\text{H}_{16}\text{O}_2$ requires C = 74.97, H = 8.38%, Found: C = 74.91, H = 8.31%.

5.10 (+)-4*R*-ethyl-4-acetyl-3-methyl-2-cyclohexanone, **R-48**

Following the general procedure, the compound **R-48** was prepared as a liquid by asymmetric cyclization of acyclic prochiral trione **47**. Yield: 45%; IR (CHCl_3), cm^{-1} : 1705 (saturated carbonyl); 1675 (conjugated carbonyl); 1615 (olefinic bond); ^1H NMR

d 6.01 (*s*, 1H, vinylic proton); 2.28 (*s*, 3H, $-\text{COCH}_3$), 1.92 (*s*, 3H, *b*-vinylic $-\text{CH}_3$), 1.82–2.52 (*m*, 6H, methylene protons), 0.98 (*t*, 3H, CH_3CH_2-); ^{13}C NMR **d** 207.93, 197.23, 160.83, 129.55, 56.76, 34.55, 30.74, 28.19, 26.35, 20.84, 8.53; $[\alpha]_{\text{D}}^{25}$: $+9^\circ$ (C, 3.1, benzene); MS (*m/z*): 180 (M^+); Analysis: $\text{C}_{11}\text{H}_{16}\text{O}_2$ requires C = 73.29, H = 8.95%; Found: C = 73.31, H = 8.99%.

5.11 (+)-*1S*-cyclohex-2-ene spirocyclopentane-2,4-dione, **S-59**

Following the general procedure, the compound **S-59** was obtained as a liquid by cyclization of (\pm)-**54** in the *neat*. Yield: 39–53%; IR (CHCl_3), cm^{-1} : 1730 (saturated carbonyl); 1680 (conjugated carbonyl); 1600 (olefinic bond); ^1H NMR **d** 6.89 (*d*, $J = 10$ Hz, 1H, *b*-vinylic proton), 5.58 (*d*, $J = 10$ Hz, 1H, *a*-vinylic proton); 1.22–2.41 (*m*, 10H, methylene protons); ^{13}C NMR **d** 203.85, 198.81, 151.10, 129.61, 52.15, 34.37, 33.43, 30.14, 26.42 and 25.40; $[\alpha]_{\text{D}}^{25}$: $+4.8^\circ$ (C, 2.9, methanol); *e/e* 29.04% MS (*m/z*): 164 (M^+); CD (nm): (q_{obs})₃₁₀ = $+22.4 \times 10^{-3}$ deg (C = 0.005, dioxane), (q_{obs})₂₇₇ = $+11.4 \times 10^{-3}$ deg (C = 0.005, dioxane); Analysis: $\text{C}_{10}\text{H}_{12}\text{O}_2$ requires C = 73.15, H = 7.37; Found: C = 73.50, H = 7.41%.

5.12 (+)-*1S*-cyclohex-2-ene spirocycloheptane-2,4-dione, **S-61**

Following the general procedure, the compound **S-61** was obtained by cyclization of (\pm)-**56** in solvent-free condition. Yield: 53–55%; IR (CHCl_3), cm^{-1} : 1710 (saturated carbonyl); 1690 (conjugated carbonyl); 1600 (olefinic bond); ^1H NMR **d** 6.91 (*d*, $J = 10.5$ Hz, 1H, *b*-vinylic proton), 6.05 (*d*, $J = 10.5$ Hz, 1H, *a*-vinylic proton); 1.40–2.85 (*m*, 10H, methylene protons); ^{13}C NMR **d** 210.99, 197.01, 150.32, 128.34, 52.64, 39.38, 35.48, 33.27, 30.79, 29.43, 25.79, 23.71; $[\alpha]_{\text{D}}^{25}$: $+1.42^\circ$ (C, 2, methanol); *e/e* 4.2% MS (*m/z*): 192 (M^+); CD (nm): (q_{obs})₃₁₃ = -2.8×10^{-3} deg (C = 0.005, dioxane), (q_{obs})₂₆₁ = $+10.1 \times 10^{-3}$ deg (C = 0.005, dioxane), (q_{obs})₂₂₇ = $+6.5 \times 10^{-3}$ deg (C = 0.005, dioxane); Analysis: $\text{C}_{12}\text{H}_{16}\text{O}_2$ requires C = 74.97, H = 8.39%; Found: C = 75.01, H = 8.41%.

5.13 (+)-*1S*-cyclohex-2-ene spirocyclooctane-2,4-dione, **S-62**

Following the general procedure, the compound **S-62** was obtained as a liquid by cyclization of (\pm)-**57** in the *neat*. Yield: 52–61%; IR (CHCl_3), cm^{-1} : 1712 (saturated carbonyl); 1695 (conjugated carbonyl); 1600 (olefinic bond); ^1H NMR **d** 6.89 (*d*, $J = 10.25$ Hz, 1H, *b*-vinylic proton), 6.09 (*d*, $J = 10.25$ Hz, 1H, *a*-vinylic proton); 1.25–2.64 (*m*, 16H, methylene protons); ^{13}C NMR **d** 215.88, 198.57, 150.25, 129.92, 52.36, 37.20, 33.90, 33.50, 30.10, 30.05, 29.61, 25.74, 24.46; $[\alpha]_{\text{D}}^{25}$: $+29.15^\circ$ (C, 12.8, benzene); MS (*m/z*): 206 (M^+); CD (nm): (q_{obs})₃₀₄ = $+87.3 \times 10^{-3}$ deg (C = 0.006, dioxane), (q_{obs})₃₄₃ = -14.7×10^{-3} deg (C = 0.006, dioxane); Analysis: $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires C = 75.68, H = 8.79%; Found: C = 75.59, H = 8.83%.

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