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Stereoselective synthesis and semiempirical studies of spiro bridgehead bicyclic N-heterocycles *via* 1,3-dipolar cycloaddition reactions of azomethine ylides

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The reaction of acenaphthylene-1,2-dione with chiral cyclic secondary α-amino acids *viz.* L-proline gives rise to the intermediate azomethine ylide which has been trapped by acetylenic and ethylenic dipolarophiles to produce bridgehead bicyclic cycloadducts. The stereoselectivity of these cycloadditions have been ascertained by semiempirical calculations. The newly synthesized spiroazabicyclic compounds have been characterized by elemental analyses and spectral techniques (IR, ^{1}H NMR, ^{13}C NMR and Mass).

Keywords: Stereoselective synthesis, semiempirical study, spiro bridgehead bicyclic heterocyclics, cycloaddition reaction, azomethine ylides

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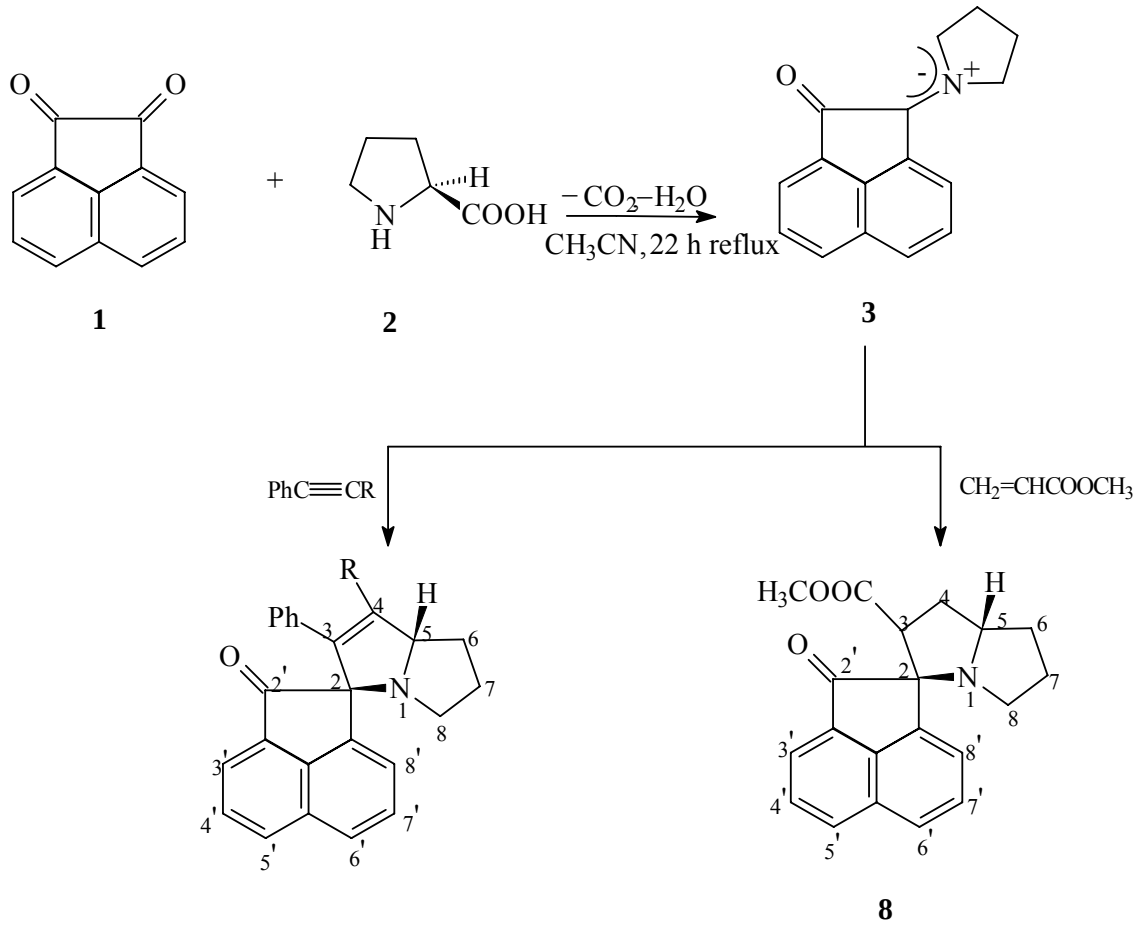
1,3-Dipolar cycloaddition reaction constitutes a core reaction resource in heterocyclic chemistry[1,2]. 1,3-dipolar cycloaddtion of azomethine ylides with dipolarophiles provides a versatile route for preparation of pyrrolidine nucleus in a single step process[3]. Azomethine ylides are powerful synthetic tools to obtain pyrrolidine derivatives having nitrogen atom as bridgehead, in a convergent and stereocontrolled manner[4]. The synthetic appeal of this strategy lies in its simplicity as it is free from side reactions and possibility of spiroheterocyclic systems being generated in a single step. Extensive literature survey revealed that cyclocondensation[5], Diels-Alder[6] and 1,3-dipolar cycloaddition reactions of acenaphthylene-1,2-dione with primary amines[7] and nitrile oxides[8] have been examined. However, 1,3-dipolar cycloaddition reactions of L-proline with α-diones have remained unexplored. The [3+2]-cycloaddition reactions of indol-2,3-dione with (*R*)-(-)-thiazolidine-4-carboxylic acid[9-11] and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid have been previously reported[12]. Thus, in continuation to our work on 1,3-dipolar cycloaddition reactions we have applied this strategy to acenaphthylene-1,2-dione with L-proline to produce bridgehead bicyclic N-heterocycles which may serve as useful precursors for synthesis of naturally occurring alkaloids[13].

The reaction of acenaphthylene-1,2-dione **1** with L-proline **2** was carried out in equimolar ratio in presence of phenyl acetylene, phenyl propyne, diphenyl acetylene, ethyl phenyl propiolate and methyl acrylate to afford (2*R*, 5*S*)-spiro-{1-aza-3-phenyl-bicyclo[3.3.0]-3-octen-2,1′-acenaphthylene}-2′-one **4**, (2*R*,5*S*)-spiro-{1-aza-4-methyl-3-phenyl bicyclo [3.3.0] -3-octen-2,1′-acenaphthylene}-2′-one **5**, (2*R*, 5*S*)-spiro-{1-aza-3, 4-diphenyl-bicyclo[3.3.0]-3-octen-2,1′-acenaphthylene}-2′-one **6**, (2*R*, 5*S*)-spiro-{1 - aza -4-ethoxycarbonyl-3-phenyl-bicyclo[3.3.0]-3-octen-2,1′-acenaphthylene}-2′-one **7** and (2*S*,3*R*,5*S*)-spiro-{1-aza-3-methoxycarbonyl-bicyclo-[3.3.0]-octan-2,1′-acenaphthylene}-2′-one **8** respectively in 68-80% yield (**Scheme I**). The mechanism involves the formation of intermediate azomethine ylide **3** (abbreviated as amy) as reported by Grigg *et al*[14]. in the reaction of carbonyl compounds with amines. Subsequently, [3+2] cycloaddition with various dipolarophiles gives the desired cycloadducts with bridgehead nitrogen atom.

The structure of the compounds **4-8** has been unambiguously established from their spectral data. In the IR spectrum of compound **8,** characteristic bands observed at 3015 and 1710 cm^{-1} have been assigned to aromatic C-H and >C=O vibrations and the absorption bands for C-N and C-O linkages were seen at 1350



Scheme I

and 1120 cm^{-1} respectively. The ^1H NMR spectrum of **8** showed a quintet at δ 1.62 (7-H), a quartet at 1.87 (6-H), another quartet at 2.30 (4-H), two triplets at 2.48 (3-H) and 2.52 (8-H), a singlet at 3.90 for methoxy protons, a quintet at 3.99 (5-H) and a multiplet in the region of 7.43-8.13 ppm for aromatic protons. Its ^{13}C NMR spectrum showed the following signals: two carbonyl carbons at δ 204.52 and 170.03, aromatic carbons in the region of 141.03-120.55, spiro carbon at 75.33, C-5 carbon at 64.43, C-8 at 54.89, methoxy carbons at 50.09, C-3 at 46.43, C-4 carbon at 33.58, C-6 at 31.27, and C-7 at 27.46 ppm.

Additional evidence was obtained from the mass spectrum of **8** which showed molecular ion peak $[M^+]$ at m/z 321 $(C_{20}H_{19}NO_3)^{+\cdot}$, fragment ion peak at m/z 262 $(C_{19}H_{16}NO)^+$ by loss of methoxy carbonyl species ($COOCH_3$) and base peak at m/z 126 formed by the loss of CO and bicyclo octane species. Conclusive evidence for the formation of cycloadducts has been obtained by X-ray crystal structure of adduct[15]. All the assignments are in complete conformity with the proposed structures. The characterization data of all the newly synthesized products have been given in **Table I**.

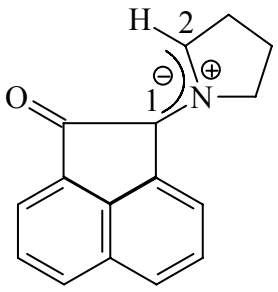
Semiempirical Molecular Orbital Studies

Semiempirical calculations have been carried out using MOPAC 6 program on AM1 hamiltonians[16,17] by using key words AM1 precise vectors. Geometry optimization showed that amy **3** has an almost planar structure. The proline ring instead of having an envelope shape, is planar and lies in the same plane as

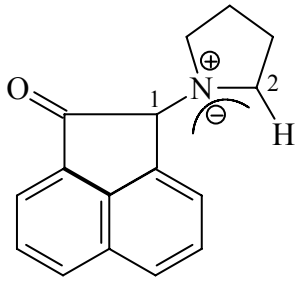
Table I — Characterization data of compounds **4-8**

Compd	Physical State	Molecular Formula	m.p. °C	Yield (%)	Found(Calcd.%) C	H	N	^{1}H NMR	^{13}C NMR
4	Brown Powder	$C_{24}H_{19}NO$	>260	68	85.21 (85.46	5.38 5.64	3.97 4.15)	1.7-1.8(m,6-H+7-H,4H), 2.87 (t, 8-H,2H), 2.98 (d, 4-H,1H), 3.21(t, 5-H,1H), 6.49-7.86(m, 11×ArH)	
5	Orange crystals	$C_{25}H_{21}NO$	181	77	85.47 (85.48	5.98 5.99	3.98 4.15)	1.2(s, CH_3), 1.7-1.8(m,6-H+7-H,4H), 2.14 (t, 8-H,2H), 3.72 (t,5-H, 1H),7.38(m, 11ArH)	183.99 (>C=O), 134.34-122.47 (ArC), 77.43 (spiro C), 62.43 (C-5), 45.88 (C-8), 31.1 (C-6), 26.7 (C-7), 13.1 (CH_3)
6	Dark Brown plates	$C_{30}H_{23}NO$	170	80	87.16 (87.18	5.56 5.59	3.38 3.39)	1.8-1.9 (m, 6-H+7-H, 4H), 2.62 (t, 8-H, 2H), 3.25(t,5-H,1H), 7.11-8.07(m,16ArH)	
7	Brown powder	$C_{27}H_{23}NO_3$	190	73	79.12 (79.22	5.47 5.62	3.38 3.39)	1.42 (t, CH_3), 1.7-1.9(m,6-H+7-H,4H),3.10 (t, 8-H, 2H),4.39(q,OCH_2), 5.02 (t, 5-H,1H), 7.19-8.51(m, 11×ArH)	
8	Yellow crystals	$C_{20}H_{19}NO_3$	145	80	74.49 (74.77	5.80 5.92	4.27 4.36)	1.62 (q, 7-H,2H), 1.87 (q, 6-H,2H), 2.30 (q, 4-H,2H), 2.48 (t, 3-H,1H), 2.52(t, 8-H,2H), 3.90(s, OCH_3), 3.99(q, 5-H,1H), 7.43-8.13(m, 6ArH)	204.52 (>C=O), 170.03(O-C=O), 141.03-120.55 (10 ArC), 75.33 (Spiro C-2), 64.43 (C-5), 54.89 (C-8), 50.09 (OCH_3),46.43 (C-3), 33.58 (C-4), 31.27 (C-6), 27.46 (C-7)

*Mass spectrum of **8** (m/z): 321[$C_{20}H_{19}NO_3$]$^{+\cdot}$ [$M^{+\cdot}$] [12%], 126 [M^+-CO, $C_9H_{13}NO_2$] [100%], 262 [M^+-CO_2CH_3] [31%].



3i



3ii

that of acenaphthylene ring. It exists in two isomeric forms, one of which has the C=O group of acenaphthylene ring and C-H of the dipole *syn* (3i) and another, in which these two groups are *anti* with respect to each other (3ii).

Ethyl phenyl propiolate may approach either of the azomethine ylides with the formation of products having two chiral centres. Therefore, a total of 4+4 = 8 isomers **7a-h** are possible (**Figure 1**). Attack of ethyl phenyl propiolate on *anti* amy (**3ii**), **Figure 2** may result in the inward movement of proline ring towards acenaphthenequinone nucleus and may lead to steric crowding between acenaphthene ring and proline ring making the system unstable. It is therefore not surprising that transition state could not be located even in a single case **7e-h**.

Thus, the only possibility is attack on *syn* amy **3i** leaving only 4 isomers **7a-d** for consideration. Out of these, only two isomers **7a,b** are formed *via* a concerted mechanism. This can be explained on the basis of FMO approach. The favoured path is $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ **(Table II)**. Besides, a secondary interaction between the two phenyl rings as well as the *endo* approach also favours the formation of product **7a** and indeed we have been able to locate the transition state only in this case.

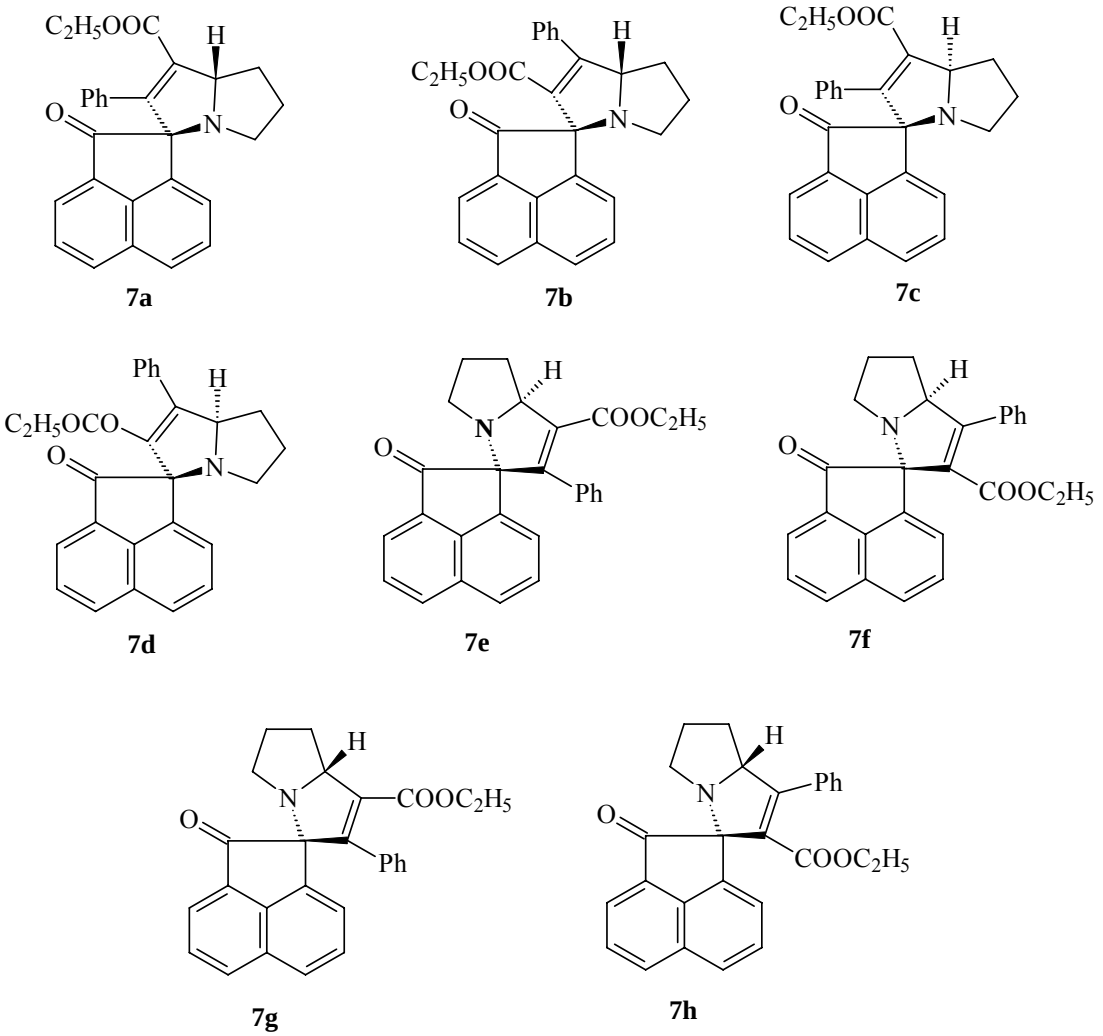


Figure 1 — Eight possible stereoisomers of the cycloadduct (**7**)

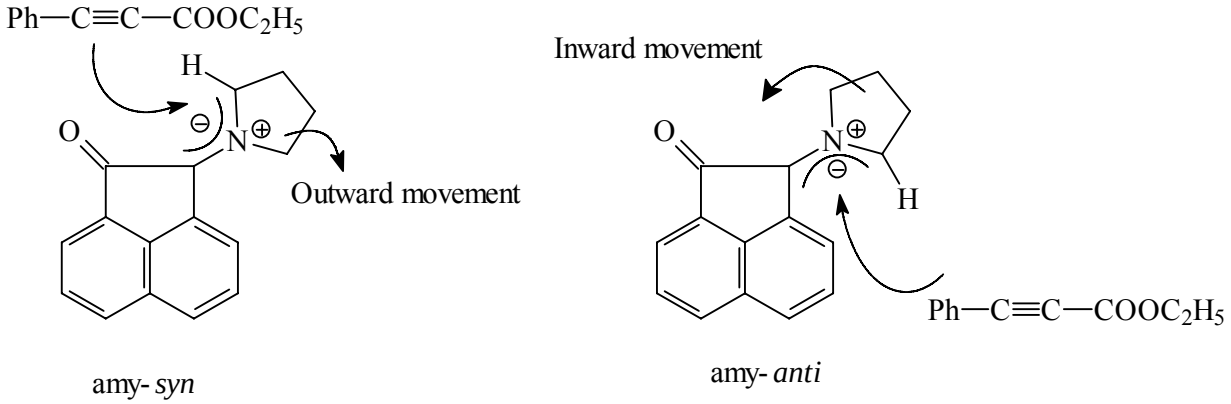


Figure 2 — Mode of the attack of dipolarophile (etph) on azomethine ylide

Parallel calculations have been performed on other cycloadducts **4-6** and the results are summarized in **Table III** and **Figure 3**. From these calculations following conclusions may be drawn:

i) Geometry optimization of the azomethine ylide **3** indicated that it has an almost planar structure. The proline ring is planar and lies in the same plane as that of the dione moiety.

Table II — ΔH_f, HOMO and LUMO energies and H-L and L-H energy gaps

	ΔH_f (Kcal/mol)	HOMO (eV)	LUMO (eV)	Energy gap (eV) H-L	L-H
DipoleAmy 3 Dipolarophile	38.41	-7.73	-0.61	-	-
Etph (7a)	-10.80	-9.71	-0.66	7.07	9.10
(7b)	7.55	-8.91	-0.74	6.99	8.30
Phac	74.65	-9.39	-0.07	7.66	8.78
Meac	-65.98	-11.06	-0.06	7.67	10.45

Amy = azomethine ylide; etph = ethyl phenyl propiolate; phac = phenyl acetylene; meac = methyl acrylate

Table III — ΔH_f-R, ΔH_f-TS, ΔH_f-P, E_a and stablization energy of amy with different dipolarophiles

Product	ΔH_f Reactant (Kcal/mol)	ΔH_f TS (Kcal/mol)	ΔH_f Product (Kcal/mol)	Energy of activation (E_a) (Kcal/mol)	Stablization energy (Kcal/mol)
Amy **3** + etph	27.59	60.45	10.20	32.86	17.29
Amy **3**+ phac	113.04	150.38	60.11	37.34	47.93
Amy **3**+ meac	-27.59	12.82	-0.85	40.41	26.74

Amy = azomethine ylide, phac = phenyl acetylene, etph = ethyl phenyl propiolate

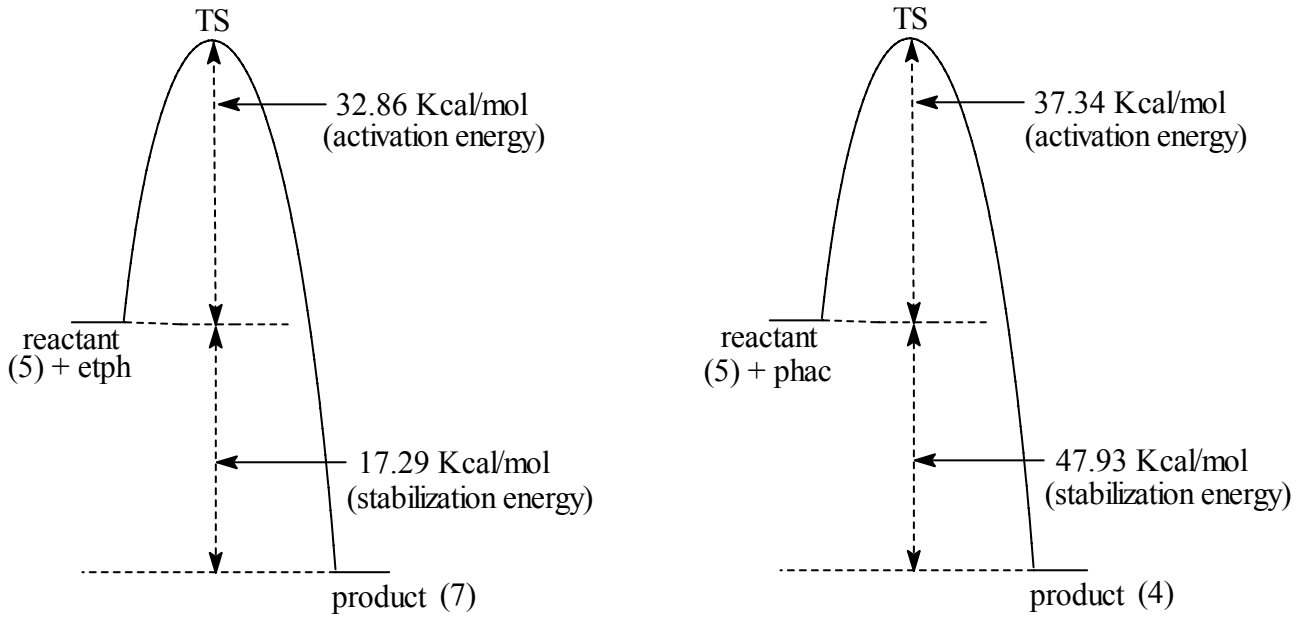


Figure 3 — Stabilization and activation energy of amy **3** with ethyl phenyl propiolate and phenyl acetylene

ii) The azomethine ylide can exist in two stereoisomeric forms *i.e. syn* and *anti*. The dipolarophile attacks on the *syn* isomer.

iii) The dominant FMO approach is $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ as this energy gap is lower than the $LUMO_{dipole}$ and the $HOMO_{dipolarophile}$ gap.

iv) The *endo approach* is favoured and the phenyl group lies towards the dione ring.

Experimental Section

All the reactions were carried out under a nitrogen atmosphere. Acetonitrile was dried by refluxing with anhydrous calcium chloride for 5-6 hr and then distilling it. Melting points of newly synthesized compounds were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on a Nicolet Magna IR Spectrometer Model 550 in KBr

pellets. The ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Brucker instrument at 300 MHz and 75.47 MHz respectively (chemical shifts in δ, ppm). Mass spectra were recorded at the Indian Institute of Chemical Technology, Hyderabad. Elemental analyses were performed on a Perkin-Elmer Series 2400 C, H, N, S Analyser. In order to purify the synthesized compounds column chromatography was performed on silica gel 60 (Merck) with solvents of rising polarity.

A representative method for the synthesis of (2*R*, 5*S*)-spiro-{1-aza-4-ethoxycarbonyl-3-phenyl-bicyclo[3.3.0]-3-octene-2,1′-acenaphthylene}-2′-one (7): A mixture of acenaphthylene-1,2-dione **1** (0.36 g, 2.0 mmoles), L-proline **2** (0.23 g, 2.0 mmoles) and ethyl phenyl propiolate (0.35 g, 2.0 mmoles) in the molar ratio of 1:1:1 was refluxed under a nitrogen atmosphere for 22 hr in dry acetonitrile (50 mL). After completion of the reaction as monitored by TLC the unreacted acid was filtered off and the reaction mixture was concentrated *in vaccuo* to half its volume and allowed to crystallise. However, no crystals appeared even after 48 hr and therefore the crude product was subjected to column chromatography over silica gel whereby chloroform-ethyl acetate (5:1) fraction afforded the compound 7 as a brown powder (0.69 g, 73%), mp 190°C.

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