Stereospecific non-decarboxylative 1,3-dipolar cycloaddition as a potential route to proline derivatives, part III[1]

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Dedicated to Professor Benito Alcaide on the occasion of his 60th birthday

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Abstract

Boiling an equimolar mixture of salicylaldehyde **1a**, DL-alanine **2a** and dimethyl fumarate **3** in acidified methanol gives a mixture of three stereoisomers **4a-c**. The effect of solvent and temperature on the diastereoselectivity is pronounced. Using fumaronitrile **13** as dipolarophile gives stereospecifically the fused tricyclic cycloadducts **16a-f**.

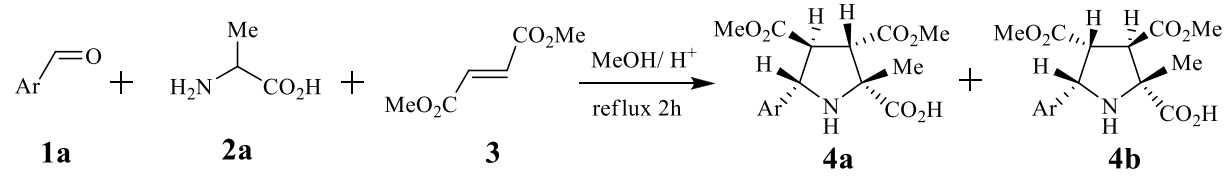
Keywords: α-Amino acids, 1,3-dipolar cycloaddition, tricyclic fused systems, spiroadducts, non-decarboxylative, thiohydantoine

Introduction

Many naturally occurring products containing the pyrrolidine ring have potent biological activities, e.g. egnicotine and kainic acid.[2] The antiinfluenza compound A-315675 is also a proline derivative.[3] During the last decade synthetic chemists have reported various methods for the synthesis of such biologically active proline derivatives.[4,5] Recently great attention has been paid to the synthesis of pyrrolidine structures, which are constituents of many natural products and pharmaceuticals.[6] We have previously reported a three component one pot synthesis to construct compounds which are closely related to kainic acid using the non-decarboxylative 1,3-dipolar cycloaddition strategy.[1,7] However, Coldham has recently reported that α-amino acids undergo a decarboxylative 1,3-dipolar cycloaddition in boiling toluene under acidic conditions.[8]

Results and Discussion

We have previously shown that acidified methanol (methanol containing a few drops of acetic acid) serves as a good solvent for non-decarboxylative 1,3-dipolar cycloaddition reactions. Thus, boiling a mixture of salicylaldehyde **1a** (Ar = 2-hydroxyphenyl), DL-alanine **2a** and dimethyl fumarate **3** in acidified methanol afforded a 1.4: 1 mixture of two isomers **4a** and **4b**, respectively in 66% combined yield (Scheme 1).[1]



Ar = 2-HOC$_6$H$_4$-

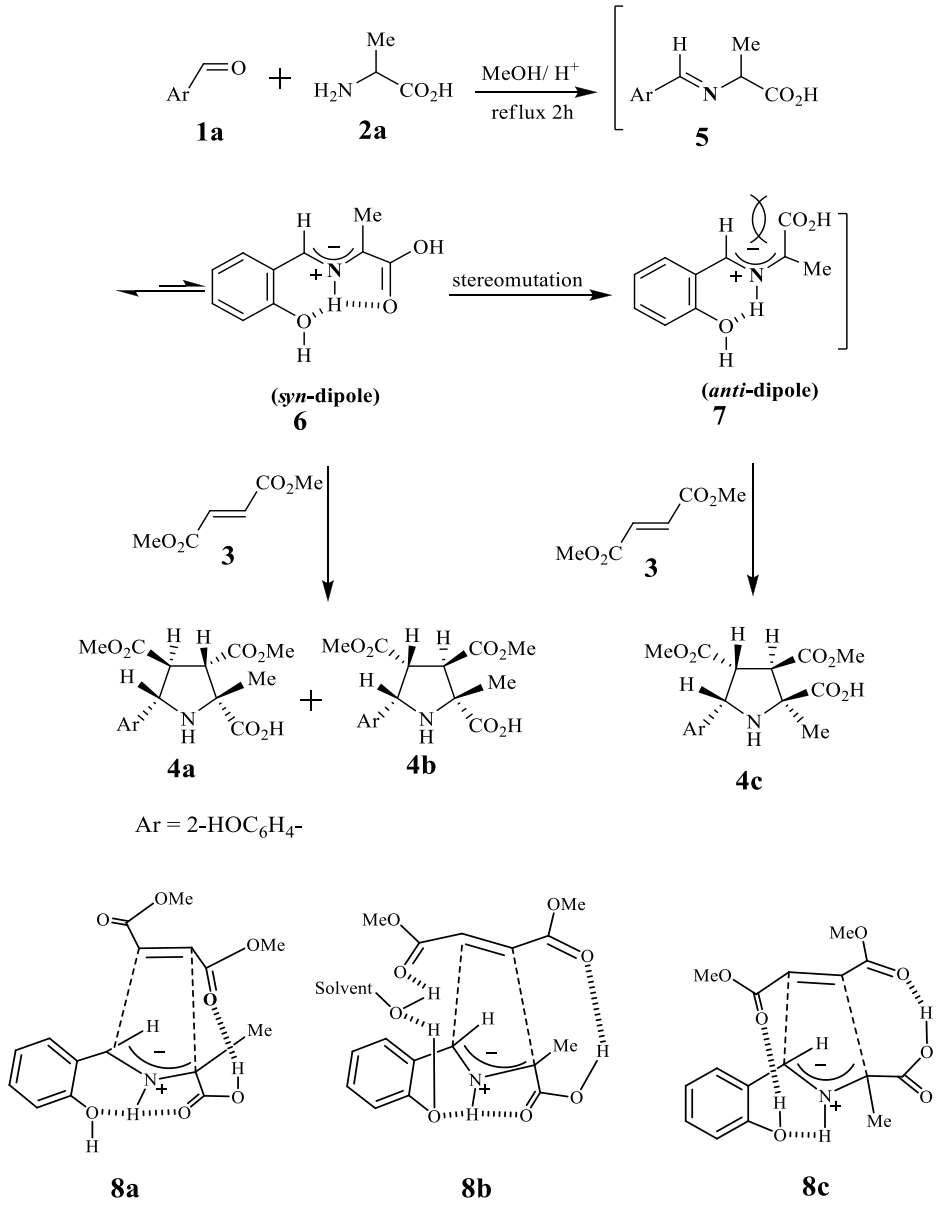
Scheme 1

Extensive ^{1}H-NMR spectroscopy studies on this reaction using more advanced spectrometers showed a third inseparable isomer **4c** which is probably obtained from the stereomutated *anti*-dipole **7**, *via* the transition state **8c**, in which both carboxyl/carboxylate and aryl/carboxylate interactions exist (Scheme 2). It seems that temperature affects the stereochemical outcome to some extent. Thus, conducting the same reaction in acidified methanol at room temperature for 2 days afforded nearly a quantitative yield (98%) of an isomeric mixture of the adducts **4a**, **4b** and **4c** in a 41: 47: 12 ratio, respectively (Table 1, entry 2). The major isomer **4b** was obtained through the transition state **8b** in which there is an additional hydrogen bonding between the phenolic group on the dipole and the carboxylate group on the dipolarophile from one side and between the carboxylic group on the dipole and the carboxylate group on the dipolarophile from the other side. Whereas, the second major isomer **4a** arose from the transition state **8a** with only hydrogen bonding between the carboxylic group on the dipole and the carboxylate group on the dipolarophile.

On the other hand, carrying out the same reaction at 0 ˚C for 2 days gave a 39% yield (calcd., ^{1}H-NMR of the crude reaction mixture) of the adducts **4a** and **4b** as the only products in a 46: 54 ratio, respectively (Table 1, entry 1). It is believed that, at low temperature the additional hydrogen bonding in the transition state **8b** is more effective which resulted in the formation of the adduct **4b** as the major isomer. At this low temperature the stereomutation of the *syn*-dipole **6** to afford the *anti*-dipole **7** was suppressed and the third isomer **4c** was not obtained. At higher temperatures, it seems that the carboxyl/carboxylate interaction in the transition state **8a** is more favorable than the aryl/carboxylate interaction in the transition state **8b**, obviously the additional hydrogen bonding is less effective at such temperature.

Interestingly, the isomeric ratio of the cycloadducts **4a**, **4b** and **4c** has been changed dramatically by using different solvents, (Table 1). Thus, using ethanol as a solvent has slightly

increased the ratio of the isomer **4a** (Table 1, entry 4), this probably in part due to the hydrogen bonding between the solvent and the phenolic group which may restrict the approach of the carboxylate group of the dipolarophile in the transition state **8b**. This was clarified by using *n*-propanol as a solvent (Table 1, entry 5), which afforded a 64% yield of the cycloadduct **4a** as the only product. In the latter case the relatively long hydrocarbon side chain of *n*-propanol has prevented the approach of the carboxylate on the dipolarophile in the transition state **8b**. The same effect was observed in AcOH,[9] THF, THF/H_2O, MeCN/H_2O (Table 2, entries 6-9). The observed modest yields are mainly due to solubility problems in THF, THF/H_2O, MeCN/H_2O and the harsh conditions in the case of AcOH.



Scheme 2

Table 1. The effect of solvent and temperature

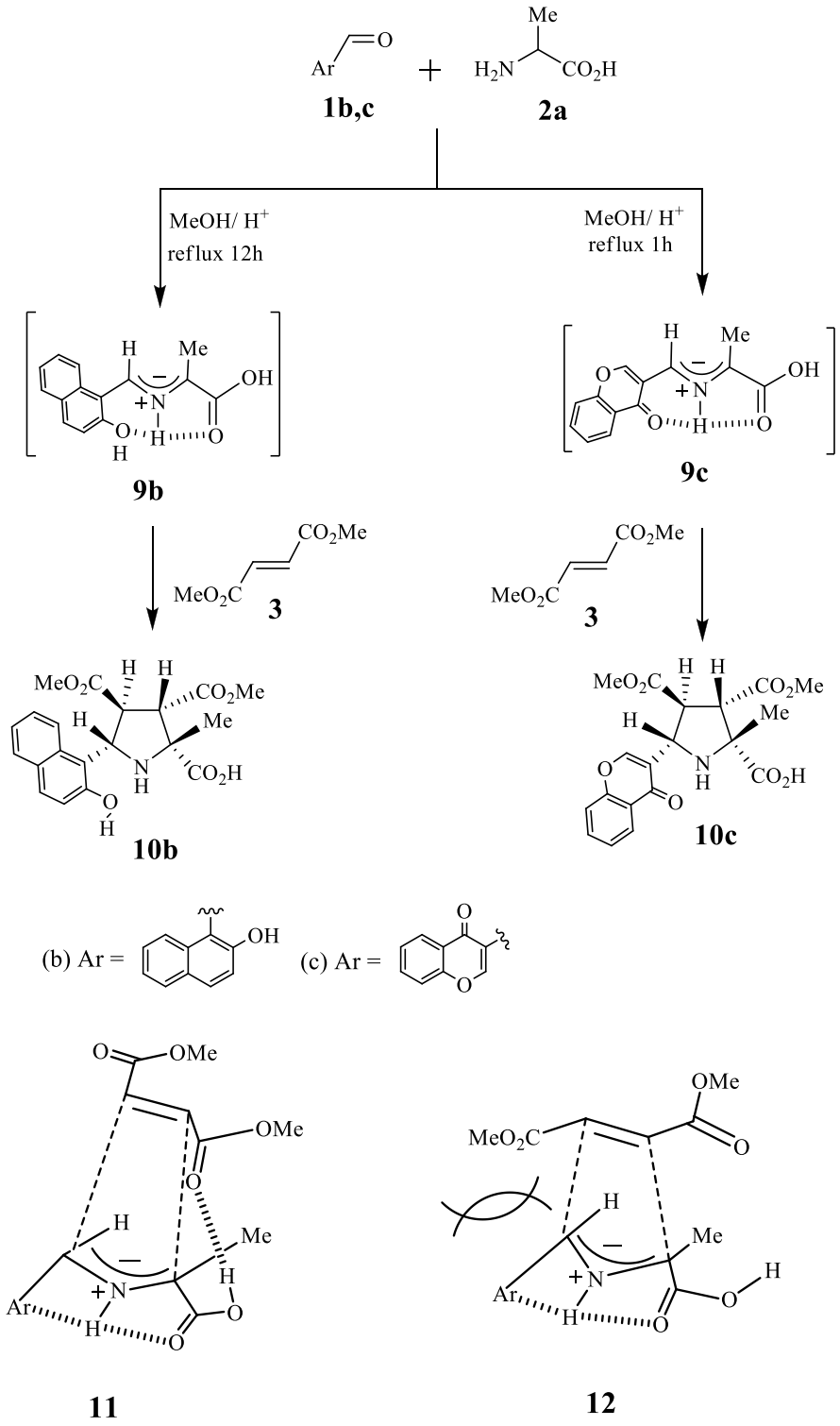
Entry	Solvent[a]	Time (h)	Yield (%)	Ratio, **4a**: **4b**: **4c**
1	MeOH[b]	48	39	46: 54: 0
2	MeOH[c]	48	98	41: 47: 12
3	MeOH	2	66	50: 40: 10
4	EtOH	2	56	57: 29: 14
5	*n*-PrOH	2	64	100: 0: 0
6	AcOH[9]	1	38	100: 0: 0
7	THF	18	37	100: 0: 0
8	THF/H_2O	18	27	100: 0: 0
9	MeCN/H_2O	18	39	100: 0: 0

[a]The reaction was conducted in boiling sovent. [b]The reaction was conducted at 0 ºC. [c]The reaction was conducted at 30 ºC.

It seems that the bulkiness of the carbonyl component in such reaction affects both the chemical yield and the stereochemical outcome to a greater extent. Thus, using 2-hydroxy-1-naphthaldehyde **1b** and 3-formylchromone **1c**[10] as carbonyl components afforded the stereospecific cycloadducts **10b** and **10c** in 40 and 60% yield, respectively, (Scheme 3). The adducts **10b,c** were formed through the transition state **11**, the other transition state **12** was ruled out on steric grounds. The stereochemistry of the adducts **10b,c** was assigned on the basis of its spectral and analytical data. Thus, ^{1}H-NMR spectrum of the cycloadducts **10b,c** show coupling constants similar to the well established cycloadduct **4a** (Table 2).

Table 2. Coupling constants for cycloadducts

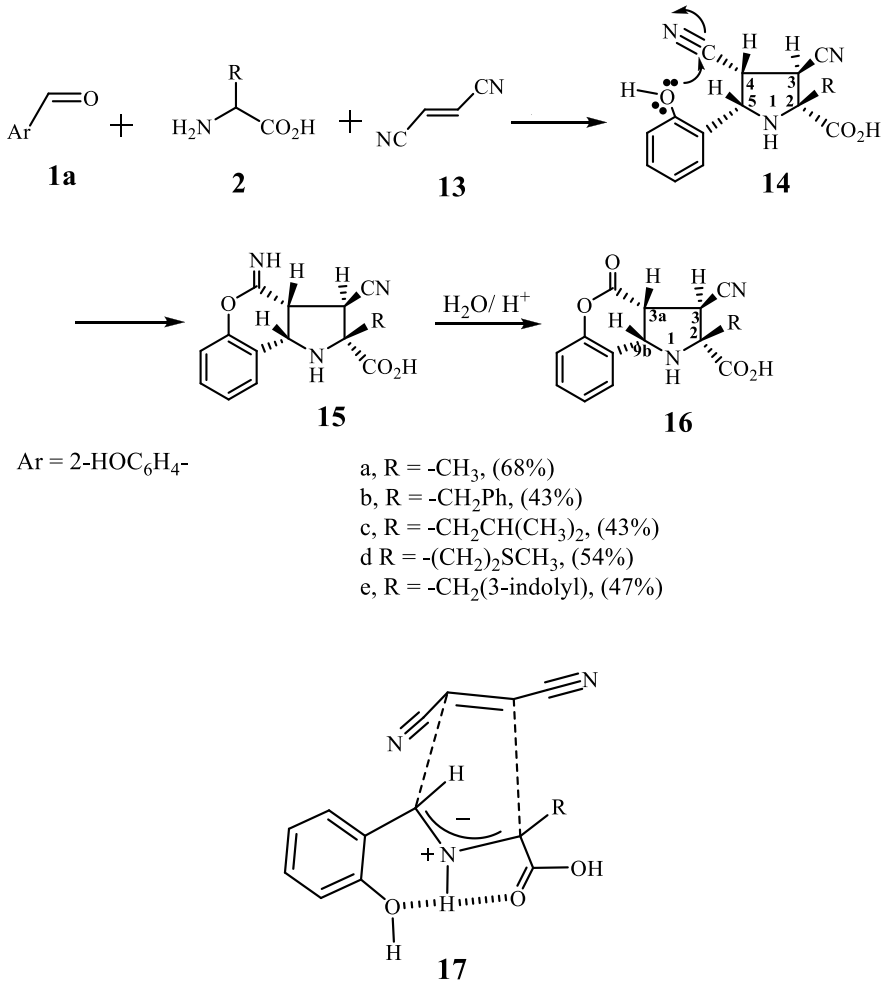
Cycloadduct	d, H_3	t, H_4	d, H_5
	$J_{3,4}$ (Hz)	$J_{3,4}$, $J_{4,5}$ (Hz)	$J_{3,4}$ (Hz)
4a	9	9.3, 10.8	10.8
10b	9	9, 10.8	10.5
10c	9.6	9.6, 10.2	10.8



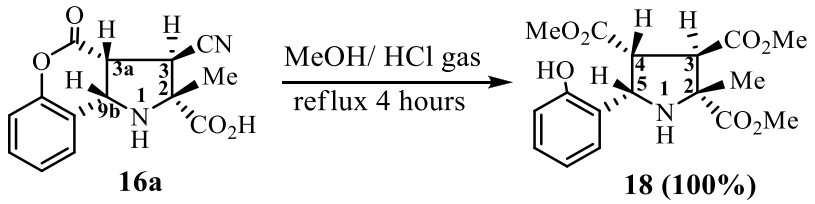
Scheme 3

Surprisingly, stirring an equimolar ratio mixture of salicylaldehyde **1a**, the appropriate α-amino acid **2a-e** and fumaronitrile **13** in an acidified methanol at ambient temperature for 48h

afforded stereospecifically the cycloadducts **16a-e** in moderate to reasonable yields 43-68% (Scheme 4). The stereochemistry of the obtained products **16a-e** was established on the basis of spectral data, and by comparison with similar systems.[8,11] Further more, boiling the cycloadduct **16a** in dry methanol saturated with HCl gas for 4h afforded a quantitative yield of the trimethyl tricarboxylate ester **18** (Scheme 5). The stereochemistry of **18** was assigned on the basis of spectral data, and by comparison with similar systems.[12] It is believed that the cycloaddition process occurs first to give the cycloadducts **14a-e**, which simultaneously resulted in **15a-e** under the reaction conditions, that finally afforded the fused-tricycles **16a-e**. However, treating salicylaldehyde and fumaronitrile under the same reaction conditions for even one week failed to give any products and the unreacted starting materials were totally recovered. In the pyrrolidine derivatives **14a-e**, the cyano group at C-4 and the hydroxyphenyl group at C-5 must have a *cis* relationship to allow the formation of the cyclic intermediates **15a-e**. Our results showed that the aryl (dipole)/cyano (dipolarophile) interaction in the transition state **17** is more effective than the carboxylate (dipole)/cyano (dipolarophile) interaction, which is in contrast with some related work reported by Grigg's group.[12]

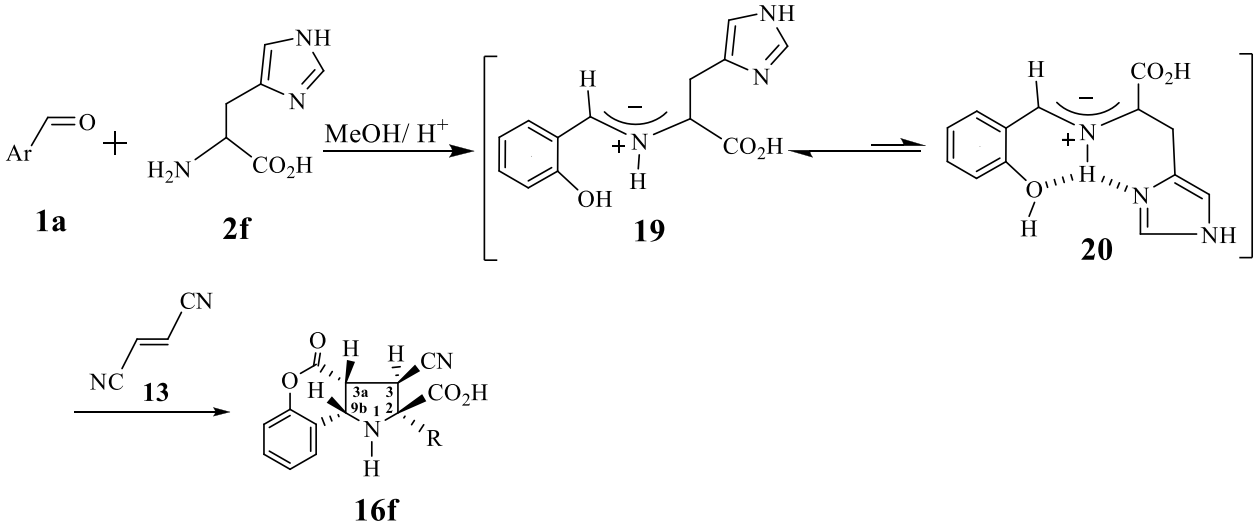


Scheme 4



Scheme 5

Interestingly, stirring an equimolar mixture of salicylaldehyde **1a**, L-histidine **2f** and fumaronitrile **13** under the same conditions gave the cycloadduct **16f** in a 43% yield as the only product, (Scheme 6). The stereochemistry of the cycloadduct **16f** was established on the basis of its spectral data, thus the ^{1}H-NMR ($CDCl_3$/TFA) spectrum showed down field doublets for both H_3 and H_{9b} compared to the same protons in the other adducts **16a-e** (Table 3). We believe that the adduct **16f** is obtained *via* the stereomutated 1,3-dipole **20**, in which the imidazolyle nitrogen atom would serve as an excellent candidate for the stabilizing bifocal hydrogen bonding.



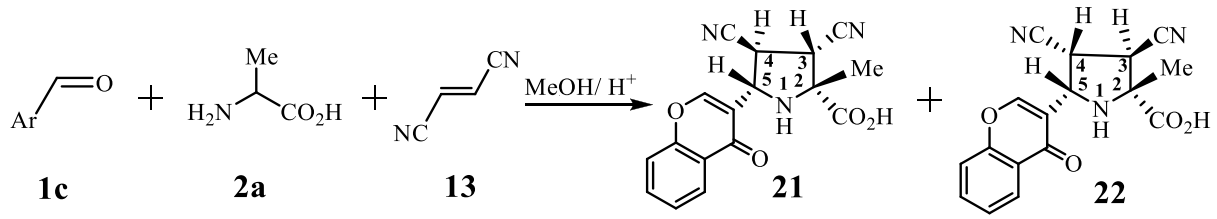
Ar = 2-HOC_6H_4-, R = -CH_2(4-imidazolyl), (43%)

Scheme 6

Table 3. ^{1}H NMR data for **16a-f**

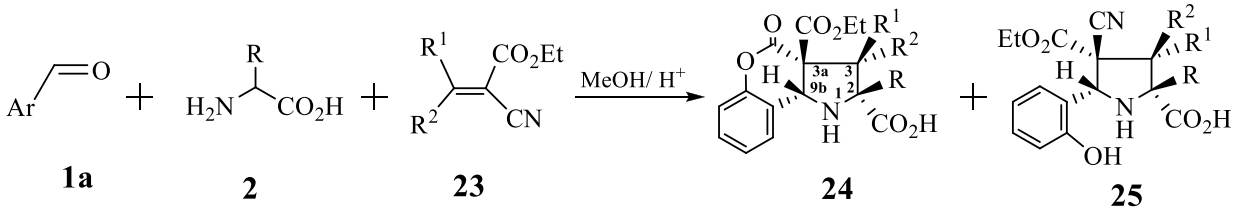
Cycloadduct	d, H_3		H_{3a}		d, H_{9b}	
	δ (ppm)	$J_{3,3a}$ (Hz)	δ (ppm)	$J_{3,3a}$, $J_{3a,3b}$ (Hz)	δ (ppm)	$J_{3a,9b}$ (Hz)
16a	3.96	11.7	4.44	t	5.29	11.4
16b	4.05	11.7	4.33	t	4.59	11.7
16c	3.97	11.7	4.39	t	5.30	12.0
16d	3.95	9.3	4.42	dd (9.0, 11.4)	5.17	11.7
16e	4.25	11.1	4.41	t	4.73	11.7
16f	4.83	6.0	4.39	dd (6.3, 8.1)	5.66	8.4

3-Formylchromone **1c** as a carbonyl component reacted in a similar manner with DL-alanine **2a** and fumaronitrile **13** leads to 61% yield of an isomeric mixture of the corresponding dicyano adducts **21** and **22** in a 4.5: 1 ratio, respectively (Scheme 7). The minor isomer **22** was separated in pure state. The stereochemistry of **21** and **22** was established on spectral data. The cycloaddition process revealed that the carboxylic (dipole)/cyano (dipolarophile) interaction in the transition state is more effective than the chromonyl (dipole)/cyano (dipolarophile) interaction, which is in agreement with the reported hypothesis.[12] This is probably due to the bulkiness of the chromonyl group.



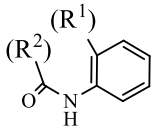
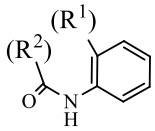
Scheme 7

Analogously, DL-alanine **2a** reacted smoothly with salicylaldehyde **1a** in the presence of *trans*-α-cyanocinnamates ethyl esters **23a-d** under the same conditions to afford the *endo*-cycloadducts **24a-d** in acceptable to good yields 47-71% together with traces of inseparable isomer in each case (Scheme 8). The stereochemistry of the obtained products was assigned on the basis of spectral data.



1a **2** **23** **24** **25**

Ar = 2-HOC_6H_4-

a, R = Me, R^1 = H, R^2 = C_6H_5 (100: 0, 64%)
b, R = Me, R^1 = H, R^2 = *p*-ClC_6H_4 (100: 0, 61%)
c, R = Me, R^1 = H, R^2 = *p*-$NO_2C_6H_4$ (100: 0, 71%)
d, R = Me, R^1 = H, R^2 = *p*-$MeOC_6H_4$ (100: 0, 47%)
e, R = Me,  , (4.5: 1, 53%)
f, R = CH_2Ph,  , (100: 0, 47%)

Scheme 8

On the other hand, stirring an equimolar mixture of DL-alanine **2a** (R = Me) with salicylaldehyde **1a** and ethyl *(2E)*-cyano-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetate **23e** in acidified methanol afforded a 53% yield of an isomeric mixture of the spiroadducts **24e** and **25e** in a 4.5: 1 ratio, respectively. Unfortunately, all attempts to separate this mixture were unsuccessful. It is worth mentioning that the ^{1}H-NMR spectrum ($CDCl_3$/TFA) of the reaction mixture (Figure 1) showed two double quartets for the C-4 ethyl ester methylene protons of the minor isomer **25e** at δ = 4.50 and 4.30 ppm, whilst the ethyl ester methylene protons at C-3a of the major isomer **24e** appeared as two double quartets at δ = 4.19 and 4.10 ppm. However, D-phenylalanine **2b** reacted similarly with **1a** and **23e** to give stereospecifically the *endo*-adduct **24f** in a 47% yield, whose ^{1}H-NMR spectrum ($CDCl_3$/TFA) (Figure 2) showed two double quartets at δ = 4.25 and 4.14 ppm for the C-3a ethyl ester methylene protons. The stereochemistry of the obtained adducts was confirmed by their spectral data.

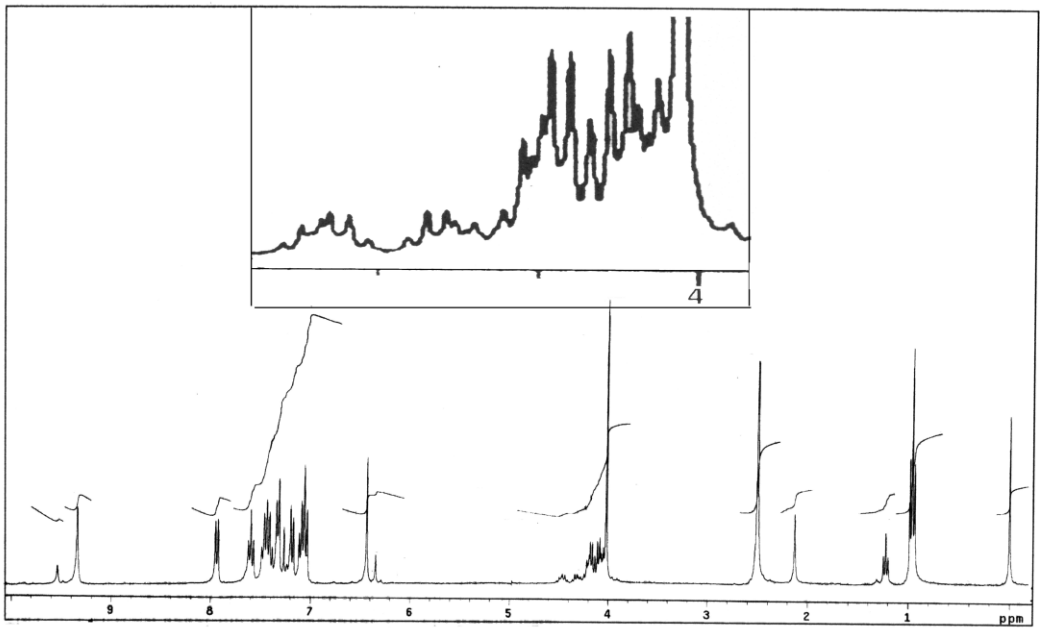


Figure 1. ^{1}H NMR spectrum of a reaction mixture containing **24e** and **25e**.

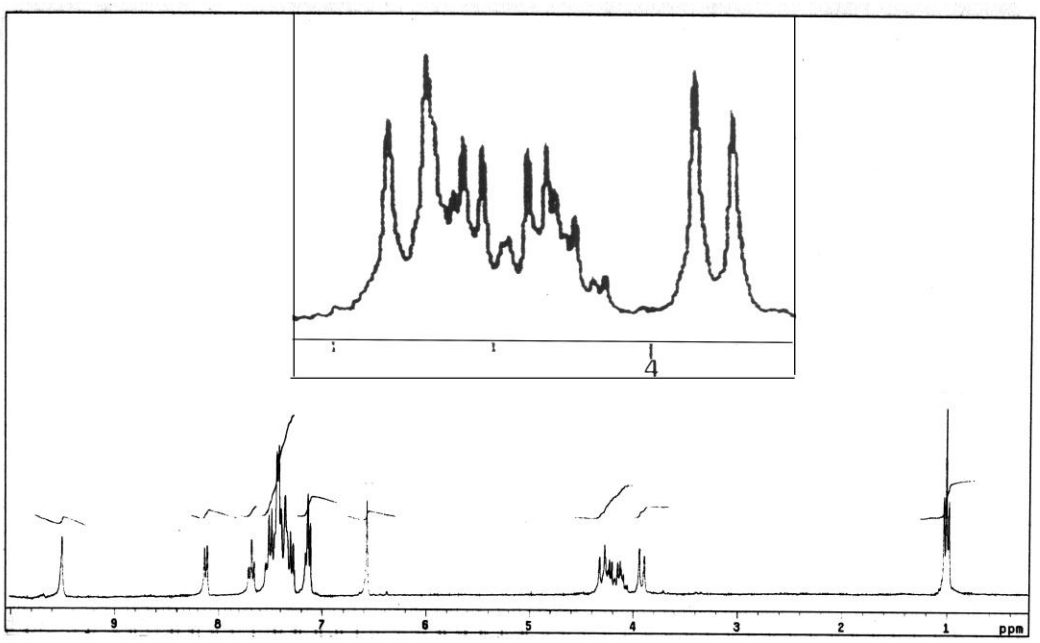
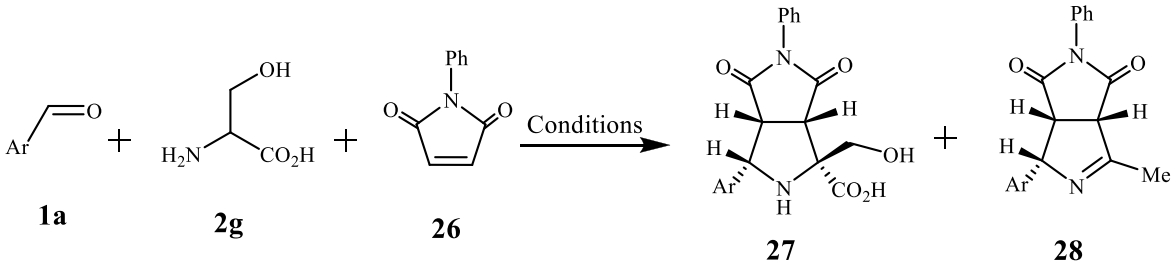


Figure 2. ^{1}H NMR spectrum of **24f**.

Grigg has reported that heating a mixture of salicylaldehyde **1a**, DL-serine **2g** and *N*-phenylmaleimide **26** in acetic acid at 100°C for 15 minutes afforded an inseparable mixture of the cycloadducts **27** and **28** in a 8: 3 ratio, respectively (unreported yield), (Scheme 9).[13] However, conducting the same reaction in boiling methanol containing a few drops of acetic acid

for 10 hours gave a 80% yield of the cycloadduct **27** as the only product. Moreover, the same mixture was boiled in a mixed solvent (methanol/toluene, 1: 1) in the presence of acetic acid (catalytic amount) to give stereospecifically the cycloadduct **27**, as the sole product in a better yield (86%) after only 2 hours (Scheme 9).



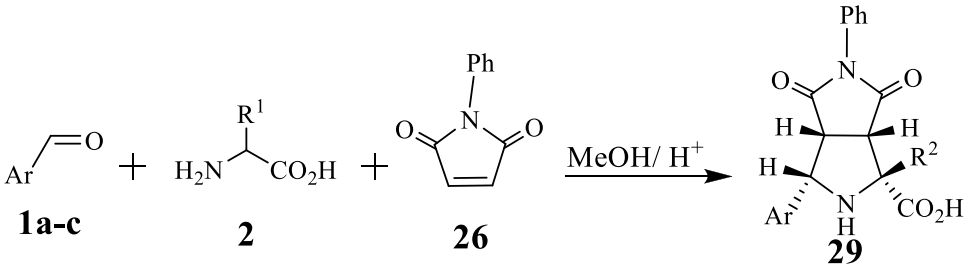
1a **2g** **26** **27** **28**

Ar = 2-HOC_6H_4-,
Conditions: (a) AcOH, 100℃, 15min, 8: 3, unreported yield.
(b) MeOH/H^+, reflux 10h, 100: 0, 80%.
(c) MeOH/Toluene + drops of AcOH (1: 1), reflux 2h, 100: 0, 86%.

Scheme 9

It was reported that the Schiff bases of a histadine tethered resin reacted with *N*-substitutedmaleimides to give isomeric mixtures of the corresponding cycloadducts (four isomers) in modest to good yields (31-82%).[14] Using our methodology, salicylaldehyde **1a** reacted with L-histidine **2** (R^1 = CH_2(4-imidazolyl)) and *N*-phenylmaleimide **26** to give the stereospecific *endo*-adduct **29a** in a 79% yield, (Scheme 10). The stereochemistry of **29a** was assigned on the basis of the spectral and analytical data and by comparison with related systems.[14] In this case the *N*-phenylmaleimide **26** (a very reactive dipolarophile) cycloadded to the kinetically obtained dipole **19** (cf. Scheme 6), meaning that the rate of cycloaddition is much faster than the stereomutation process. Analogously, 2-hydroxy-1-naphthaldehyde **1b** reacted smoothly with DL-alanine **2** (R^1 = Me) and *N*-phenylmaleimide **26** under the same conditions to give a 95% yield of the *endo*-adduct **29b**. Similarly, the reaction of 3-formylchromone **1c** with both DL-alanine **2** (R^1 = Me) and glycine **2** (R^1 = H) in the presence of *N*-phenylmaleimide **26** gave in a stereospecific manner the cycloadducts **29c** and **29d** in 72 and 84% yields, respectively. However, 3-formylchromone **1c** reacted smoothly with L-cysteine **2** (R^1 = CH_2SH) in the presence of *N*-phenylmaleimide **26** to give a 42% yield of the *endo*-cycloadduct **29e** as the only product. The stereochemistry of the stereospecific *endo*-cycloadduct **29e** was confirmed authentically, thus reacting 3-formylchromone **1c** with L-cystine **2** (R^1 = $CH_2SSCH_2CH(NH_2)COOH$) and *N*-phenylmaleimide **26** under the same conditions afforded a 49% of the same adduct **29e**. It is believed that in case of L-cysteine **2** (R^1 = CH_2SH) the cycloaddition occurred first and then the (-CH_2SH) at C_2 in the formed cycloadduct reacted

immediately with another molecule of L-cysteine. The chemical structure of the cycloadduct **29e** was established by its spectral and analytical data.

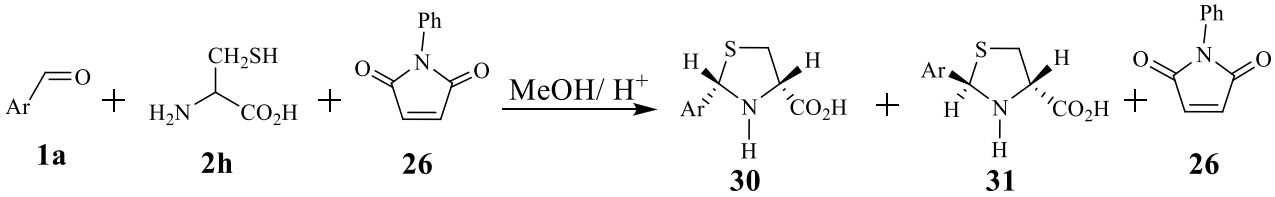


1a-c **2** **26** **29**

a, Ar = 2-hydroxyphenyl, $R^1 = R^2 = CH_2$(4-imidazolyl) (79%)
b, Ar = 2-hydroxy-1-naphthyl, $R^1 = R^2$ = Me (95%)
c, Ar = 3-chromonyl, $R^1 = R^2$ = Me (72%)
d, Ar = 3-chromonyl, $R^1 = R^2$ = H (84%)
e, Ar = 3-chromonyl, $R^1 = CH_2SH$, $R^2 = CH_2SSCH_2CH(NH_2)COOH$ (42%)

Scheme 10

On the other hand, boiling a mixture of L-cysteine **2h**, salicylaldehyde **1a** and *N*-phenylmaleimide **26** in acidified methanol afforded a quantitative yield of an isomeric mixture of the thiazolidines **30** and **31** in a 1.5: 1 ratio, respectively as the only products and the unreacted *N*-phenylmaleimide **26** was totally recovered (Scheme 11). Due to some experimental problems, the products **30** and **31** were inseparable. The stereochemistry of **30** and **31** was assigned on the basis of elemental and spectral data for the reaction mixture, and by comparison with related systems.[15] The preference of the 1,5-*endo*-*trig*-cyclization process over the 1,3-dipolar cycloaddition is mainly attributed to the bigger size and softer sulfur atom.



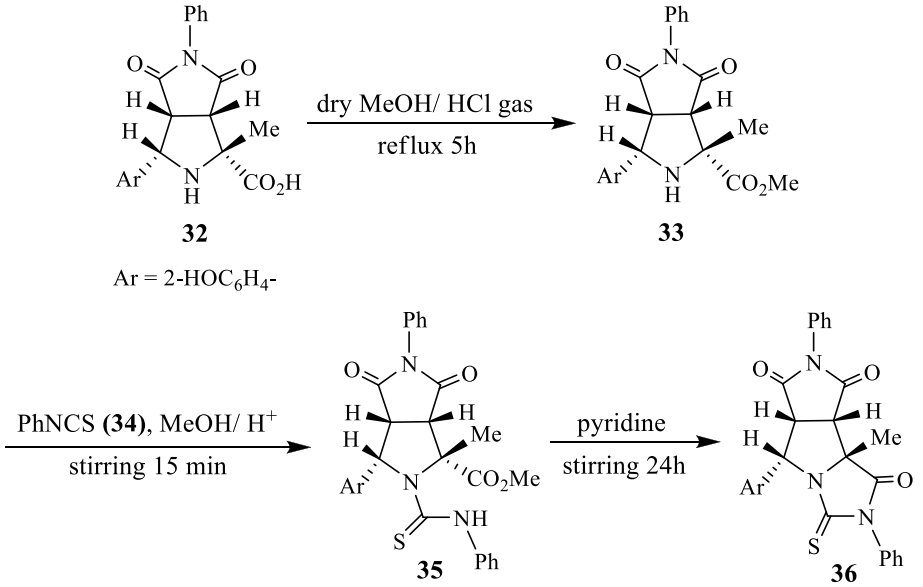
1a **2h** **26** **30** **31** **26**

Ar = 2-HOC_6H_4-

Scheme 11

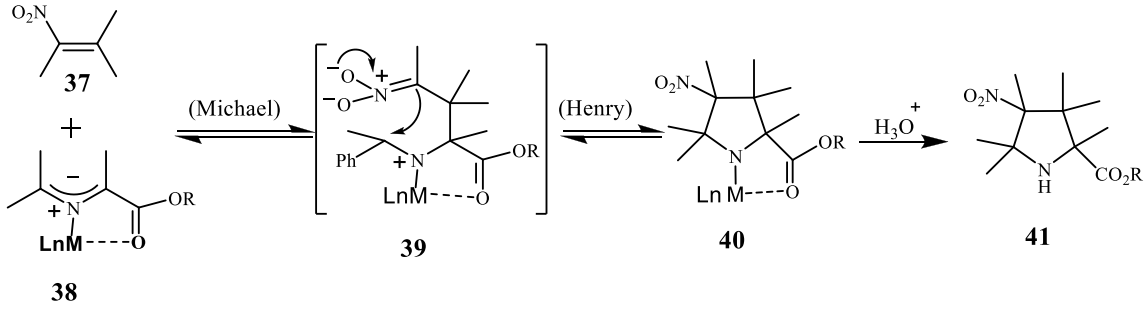
It is well known that thiohydantoins containing heterocycles have interesting biological effects.[16] It seems that the ester derivative **33** would serve well in the thiohydantoin synthesis. Boiling the carboxylic acid derivatives **32**[1] in dry MeOH saturated with HCl gas for 5 hours afforded the corresponding methyl ester **33** in a quantitative yield, (Scheme 12). The

stereochemistry of the ester **33** was established by its spectral and analytical results and by comparison with similar systems.[13,17] Reacting the obtained ester **33** with phenylisothiocyanate **34** in dry methanol afforded the thiourea derivative **35,** which on treating with pyridine at room temperature gave a quantitative yield of the corresponding thiohydantoin **36**. The thiohydantoin **36** was also obtained quantitatively *via* a one pot reaction by stirring a mixture of the ester **33** with phenylisothiocyanate **34** in pyridine for 24 hours at room temperature. The stereochemistry of compounds **35** and **36** was confirmed by their spectral and analytical data.



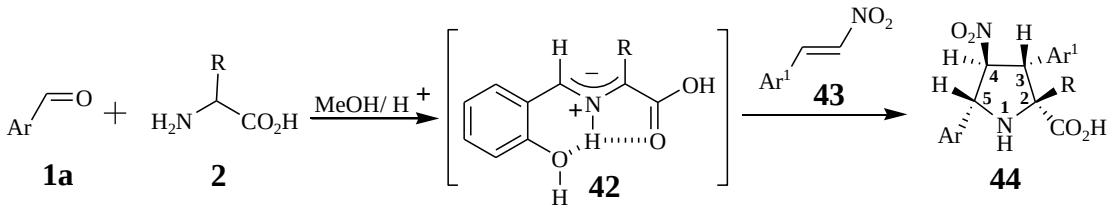
Scheme 12

Nitrostyrenes have been widely used as good dipolarophiles in the [3+2]cycloaddition reactions to give poor to moderate yields of isomeric mixtures (2-4 isomers).[4,18] Cossio[19] and others[20] in their concept showed that the adducts are formed *via* a tandem Michael-Henry reaction (Scheme 13). On the other hand, Grigg has reported that this reaction occurs through a concerted transition state.[21]

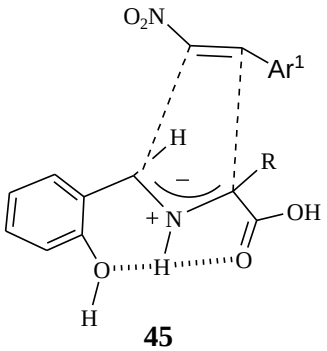


Scheme 13

However, in our laboratory, the α-amino acids **2a-d** readily reacted with salicylaldehyde **1a** and β-nitrostyrene **43** (Ar^1 = Ph) in boiling acidified methanol to give the stereospecific cycloadducts **44a-d** in moderate yields (44-53%), through the *exo*-transition state **45** (Scheme 14). The stereochemistry of the obtained adducts **44a-d** was confirmed according to the elemental and spectral data, and also by comparison with related systems.[4, 18-20] The ^{1}H-NMR spectra of the cycloadducts **44a-d** showed a down field absorption of H_4 (5.29 – 6.28 ppm) due to the deshielding effect of the nitro group (Table 3, entries a-d). However, NOE data of the cycloadduct **44a** established the suggested stereochemistry. Thus, irradiating (DMSO-d_6) 5-H results in across the ring enhancement of 3-H (3.23%), whilst irradiation of 4-H causes (1.70%) enhancement of 3-H. On the other hand irradiation of 3-H gives rise (1.70%) enhancement of 4-H, whereas it causes across the ring enhancement of 5-H (3.35%) and enhancement of 2-Me (0.50%). We believe that this reaction under our conditions undergoes a concerted 1,3-dipolar cycloaddition rather than the stepwise mechanism, as we obtained only one stereospecific adduct in each case.



(a) Ar = 2-HOC_6H_4, Ar^1 = Ph, R = Me, (53%)
(b) Ar = 2-HOC_6H_4, Ar^1 = Ph, R = -CH_2Ph, (57%)
(c) Ar = 2-HOC_6H_4, Ar^1 = Ph, R = -CH_2CHMe_2, (44%)
(d) Ar = 2-HOC_6H_4, Ar^1 = Ph, R = -CH_2CH_2SMe, (44%)
(e) Ar = 2-HOC_6H_4, Ar^1 = 2-furyl, R = Me, (45%)
(f) Ar = 2-HOC_6H_4, Ar^1 = 2-furyl, R = -CH_2Ph, (30%)
(g) Ar = 2-HOC_6H_4, Ar^1 = 2-furyl, R =-CH_2CH_2SMe, (33%)



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Scheme 14

Similarly, α-amino acids **2** (R = Me, -CH_2Ph, -CH_2CH_2SMe) reacted with salicylaldehyde **1a** and 2-[(*E*)-2-nitrovinyl]furan **43** (Ar^1 = Furyl) as a dipolarophile under the same conditions to give moderate yields (30-45%) of the corresponding adducts **44e-g**. The stereochemistry of the

cycloadducts **44e-g** was confirmed by their spectral and analytical data (Table 4, entries e-g), and by comparison with related systems. The structure of the cycloadduct **44e** was assigned in an analogous fashion based on NOE experiments, thus irradiating (DMSO-d_6) of 5-H causes across ring enhancement of 3-H (4.00%) and 2-Me (0.22%). Irradiation of 4-H results in enhancement of 3-H (1.34%) and 2-Me (1.18%). Finally irradiation of 3-H affords enhancement of 4-H (1.43%) and across ring enhancement of 5-H (2.49) and (0.75%) enhancement for the 2-Me. In general the low yields in such reactions may be attributed to the lower stability of nitrostyrenes under the acidic conditions. Attempts to use benzaldehyde, 2-methoxybenzaldehyde, *p*-nitrobenzaldehyde as carbonyl components in the above reaction failed to give the corresponding cycloadducts, and a messy complex mixture of decomposition products was obtained in each case. We still believe that the phenolic –OH group of salicylaldehyde affects greatly the cycloaddition process, due to the formation of the bifocal hydrogen bonded azomethine ylide **42**.

Table 4. ^{1}H NMR data for **44a-g**

Entry	H_3		H_4	H_5	
	δ (ppm)	$J_{3,4}$ (Hz)	δ (ppm)	δ (ppm)	$J_{4,5}$ (Hz)
a*	d, 4.32	7.8	t, 5.29	d, 5.04	8.1
b	d, 4.79	10.2	t, 6.28	d, 5.46	10.2
c	d, 4.60	10.5	t, 6.11	d, 5.47	10.5
d	d, 4.71	10.5	t, 6.24	d, 5.55	10.5
e	d, 4.79	9.0	t, 6.19	d, 5.54	9.6
f	d, 4.85	9.0	t, 6,17	d, 5.42	10.5
g	d, 4.83	9.3	t, 6.18	d, 5.56	10.2

^{1}H-NMR solvent is $CDCl_3$/TFA; * ^{1}H-NMR solvent is DMSO-d_6

Conclusions

We present herein a convenient method for the synthesis of some proline derivatives including the fused-tricyclic compounds. We have also demonstrated the effect of solvent and temperature on the diastereoselectivity.

Experimental Section

General Procedures. Proton nmr spectra were recorded at 300 MHz using Oxford nmr instrument and Varian mercury 300 MHz instrument and $CDCl_3$/TFA was used as a solvent in all cases, otherwise it is mentioned, the chemical shifts are given on the δ scale; in all cases TMS served as the internal standard. The IR spectra were measured on Shimadzu IR instrument. MS

spectra were recorded at 70ev using GCMS-QP1000EX mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240C microanalyser. Melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. The starting materials were commercially available from either Aldrich or Fluka Chemical Companies.

Method A. Heating under reflux an equimolar mixture (10 mmol) of the carbonyl component, α-amino acid and dipolarophile in acidified methanol (10 mL) for the proper time. The corresponding cycloadducts precipitated out of the hot solution. The solvent was evaporated under reduced pressure and to the obtained residue was added chloroform (10 mL) and the resulting solid was filtered off and crystallized from aqueous methanol (MeOH/H_2O, 3:2).

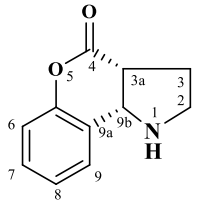
Method B. Stirring at room temperature an equimolar mixture (10 mmol) of the carbonyl component, α-amino acid and dipolarophile in acidified methanol (10 mL) for 2 days during which time the corresponding cycloadducts precipitated out of solution. The solvent was evaporated under reduced pressure and to the obtained product was added chloroform (10 mL), and the resulting solid was filtered off and crystallized from aqueous methanol (MeOH/H_2O, 3:2). The cycloadducts prepared by this method were heated at 95 ºC to get rid of the solvent (MeOH); in some cases we could not remove MeOH commpletely at this degree, e.g. the cycloadducts **16a-e**, **21**, **22** and **24e**. However, either heating at 95 ºC for a prolonged period of time or at higher temperatures resulted in decomposition.

Method C. An equimolar mixture (10 mmol) of salicylaldehyde **1a**, DL-alanine **2a** and dimethyl fumarate **3** in acidified methanol (10 mL) at 0 ºC for 2 days, by which time the corresponding cycloadducts precipitated out of solution. The solvent was evaporated under vacuum and to the obtained precipitate was added chloroform (10 mL) and the resulting solid was filtered off and crystallized from the proper solvent.

5-(2-Hydroxy-1-naphthyl)-3,4-bis(methoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (10b). According to the general procedure (method A) using 2-hydroxy-1-naphthaldehyde **1b** as carbonyl component, DL-alanine **2a** as α-amino acid and dimethyl fumarate **3** as a dipolarophile, the corresponding cycloadduct **10b** was obtained after 12 hours as colorless needles (0.155 g, 40%), mp 204-206 ºC. IR (KBr) 3737, 3373 (broad), 2370, 1700(broad), and 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.93-7.12 (m, 6H, Ar-H), 6.06 (d, 1H, *J* = 10.5 Hz, H_5), 4.34 (t, 1H, H_4), 3.97 (d, 1H, *J* = 9 Hz, H_3), 3.90 and 3.62 (2s, 6H, 2 x CO_2Me) and 2.15 (s, 3H, C-Me). Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.03; H, 5.44; N, 3.59.

3,4-Bis(methoxycarbonyl)-2-methyl-5-(4-oxo-4*H*-chromen-3-yl)pyrrolidine-2-carboxylic acid (10c). The reaction was carried out according to the general procedure (method A) using 3-formylchromone **1c** as carbonyl component, DL-alanine **2a** as α-amino acid and dimethyl fumarate **3** as a dipolarophile, the adduct **10c** was obtained after 1 hour as white powder, crystallization from aqueous methanol gave colorless fine needles (0.237 g, 61%), mp 228-230 ºC. IR (KBr) 3000 (broad), 1740 (broad), and 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.54 (s, 1H, chromonyl, -OCH-), 8.23-7.68 (m, 4H, Ar-H), 5.25 (d, 1H, *J* = 10.5 Hz, H_5), 4.24 (t, 1H,

H_4), 3.84 (d, 1H, H_3), 3.93, 3.84 (2s, 6H, 2 x CO_2Me) and 2.04 (s, 3H, C-Me). MS (*m/z* %): 388 (M-1, 6), 344 (M-45, 12), 252 (99), 244 (100), 225 (51), 186 (24), 159 (26), 115 (68), 84 (27), 77 (29) and 51 (37). Anal. Calcd for $C_{19}H_{19}NO_8$: C, 58.61; H, 4.92; N, 3.60. Found: C, 58.59; H, 4.94; N, 3.62.



3-Cyano-2-methyl-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[4,3-*b*]pyrrole-2-carboxylic acid (16a). The reaction was carried out according to the general procedure (method B) using salicylaldehyde **1a**, DL-alanine **2a** and fumaronitrile **13** to afford **16a** (0.21 g, 68%), mp 202-204 ºC. IR (KBr): 3750, 3446-2657 (broad), 2362, 2250, 1745, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.15-7.00 (m, 4H, Ar-H), 5.29 (d, 1H, *J* = 11.4 Hz, H_{9b}), 4.44 (t, 1H, H_{3a}), 3.98 (s, 3H, MeOH, solvent), 3.96 (d, 1H, *J* = 11.7 Hz, H_3) and 2.18 (s, 3H, C-Me). MS (*m/z* %): 304 (M^+, 10), 259 (75), 231 (82), 216 (46), 200 (100), 183 (34), 172 (39), 147 (55), 80 (50) and 52 (23). ^{13}C-NMR (DMSO-d_6/TFA) 169.74, 167.47, 156.15, 131.50, 129.65, 119.44, 116.27, 115.94, 115.74, 67.95, 58.17, 54.06, 52.75, 34.39, 21.51. DEPT (DMSO-d_6/TFA) 131.52, 129.66, 119.42, 115.72, 58.10, 54.03, 52.76, 34.37, 21.51. Anal. Calcd for $C_{14}H_{12}N_2O_4$.MeOH: C, 59.2; H, 5.3; N, 9.21. Found: C, 58.6; H, 5.2; N, 9.15.

2-Benzyl-3-cyano-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole-2-carboxylic acid (16b). The reaction was carried out according to the general procedure (method B) using salicylaldehyde **1a**, D-phenylalanine **2b** and fumaronitrile **13** to afford **16b** (0.16 g, 43%), mp 200-202 ºC. IR (KBr): 3737, 3609-2947 (broad), 2357, 2250, 1738, 1643 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.48-6.93 (m, 9H, Ar-H), 4.59 (d, 1H, *J* = 11.7 Hz, H_{9b}), 4.33 (t, 1H, H_{3a}), 4.05 (d, 1H, *J* = 11.7 Hz, H_3), 4.01(s, 3H, MeOH, solvent), 3.84 (d, 1H, *J* = 15.3 Hz, H_A, C-CH_2Ph) and 3.69 (d, 1H, *J* = 15.0 Hz, H_B, C-CH_2Ph). MS (*m/z* %): 275 (M-45-60, 28), 223 (19), 185 (29), 159(16), 133 (10), 106 (15), 91 (100), 77 (26), 64 (26) and 51 (22). Anal. Calcd for $C_{20}H_{16}N_2O_4$.MeOH: C, 66.3; H, 5.3; N, 7.37. Found: C, 65.9; H, 5.00; N, 7.29.

3-Cyano-2-isobutyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole-2-carboxylic acid (16c). The general procedure (method B) was applied using salicylaldedyde **1a**, L-leucine **2c** and fumaronitrile **13** to afford **16c** (0.15 g, 43%), mp 204-206 ºC. IR (KBr): 3728, 3438-2961 (broad), 2355, 2253, 1730, 1622 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.51-7.00 (m, 4H, Ar-H), 5.3 (d, 1H, *J* = 12 Hz, H_{9b}), 4.39 (t, 1H, H_{3a}), 4.01 (s, 3H, MeOH, solvent), 3.97 (d, 1H, *J* = 11.7 Hz, H_3), 2.64 (dd, 1H, *J* = 7.5 and 15.3 Hz, H_A, C-CH_2CH), 2.37 (dd, 1H, *J* = 6.0 and 15.3 Hz, H_B, C-CH_2CH), 1.91 (m, 1H, -CHMe_2), 1.06 and 1.03 (2d, 6H, *J* 6.6 Hz, -CHMe_2). MS (*m/z* %): 301 (M-44, 95), 300 (100), 241 (18), 198 (34), 191 (57), 145 (29), 115 (28), 105 (16), 77 (35) and 51 (23). Anal. Calcd for $C_{17}H_{18}N_2O_4$.MeOH: C, 62.41; H, 6.40; N, 8.09. Found: C, 62.3; H, 6.35; N, 8.00.

3-Cyano-2-[2-(methylthio)ethyl]-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]-pyrrole-2-carboxylic acid (16d). The reaction was conducted according to the general procedure (method B) using salicylaldehyde **1a**, DL-methionine **2d** and fumaronitrile **13** to give **16d** (0.2 g, 54%), mp 218-220 ºC. IR (KBr): 3734, 3366-2650 (broad), 2352, 2255, 1734, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.52-7.02 (m, 4H, Ar-H), 5.17 (d, 1H, *J* = 11.7 Hz, H_{9b}), 4.42 (dd, 1H, *J* = 9 and 11.4, H_{3a}), 3.96 (s, 3H, MeOH, solvent), 3.95(d, 1H, *J* = 9.3 Hz, H_3), 2.99-2.66 (m, 4H, C-$(CH_2)_2$-S-) and 2.23 (s, 3H, -SMe). MS (*m/z* %): 319 (M-45, 8), 242 (37), 212 (21), 198 (26), 159 (80), 145 (21), 133 (17), 90 (21), 75 (22), 61 (100) and 51 (23). Anal. Calcd for $C_{16}H_{16}N_2O_4S$.MeOH: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.00; H, 5.50; N, 7.65; S, 8.5.

3-Cyano-2-(1*H*-indol-3-ylmethyl)-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]-pyrrole-2-carboxylic acid (16e). The reaction was carried out according to the general method (method B) using salicylaldehyde **1a**, L-tryptophane **2e** and fumaronitrile **13** to produce **16e** (0.2 g, 47%), mp 236-238 ºC. IR (KBr): 3737, 3359 (broad), 2357, 2268, 1740-, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.74-6.96 (m, 10H, Ar-H and NH), 4.73 (d, 1H, *J* = 11.7 Hz, H_{9b}), 4.41 (t, 1H, H_{3a}), 4.25 (d, 1H, *J* = 11.1 Hz, H_3) 4.1 (s, 3H, MeOH, solvent), and 4.05 (d, 2H, *J* = 3.6 Hz, C-CH_2-indolyl). MS (*m/z* %): 374(M-45, 0.6), 372 (2), 315 (6), 130 (100), 116 (13), 102 (7), 76 (10) and 51 (4). Anal. Calcd for $C_{22}H_{17}N_3O_4$.MeOH: C, 65.86; H, 5.05; N, 10.02. Found: C, 65.43; H, 5.00; N, 9.88.

3-Cyano-2-(1*H*-imidazol-4-ylmethyl)-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]-pyrrole-2-carboxylic acid (16f). The general procedure (method B) was applied using salicylaldehyde **1a**, L-histidine **2f** and fumaronitrile **13** to give **16f** (0.15 g, 43%), mp 230-232 ºC. IR (KBr): 3600-2700 (broad), 2350, 2243, 1720, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.57 and 7.73 (2s, 2H, imidazolyl-H), 7.48-6.98 (m, 4H, Ar-H), 5.66 (d, 1H, *J* = 8.4 Hz, H_3), 4.83 (d, 1H, *J* = 6.0 Hz, H_{9b}), 4,39 (dd, 1H, *J* = 6.3 and 8,1 Hz, H_{3a}), 4.04 (d, 1H, *J* = 16.2 Hz, H_A, C-CH_2-imidazolyl), 3.90 (d, 1H, *J* = 15.9 Hz, H_B, C-CH_2-imidazolyl). MS (*m/z* %): 293 (M-45, 18), 275 (100), 207 (41), 184 (18), 137 (12), 82 (32), 63 (13) and 51 (11). Anal. Calcd for $C_{17}H_{14}N_4O_4$: C, 50.35; H, 4.17; N, 16.56. Found: C, 49.99; H, 4.12; N, 16.45.

5-(2-Hydroxyphenyl)-2,3,4-tri(methoxycarbonyl)-2-methylpyrrolidine (18). In two necked flask containing dry MeOH (20 mL) was added the cycloadduct **16a** (0.304 g, 10 mmol) then dry HCl gas was passed through the obtained suspension for 1h, and finally the solution was refluxed for 4 h. The reaction mixture was allowed to reach room temperature, The solvent was removed under reduced pressure and the formed amino ester hydrochloride was dissolved in CH_2Cl_2 (20 mL) and neutralized by aqueous $NaHCO_3$ (5%). The organic layer was separated and washed by water and saturated sodium chloride solution then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the trimethyl ester **18** in quantitative yield (0.35 g, 100%). Colourless needels, mp 134-136 ºC (CH_2Cl_2/pet-ether 40-60). ^{1}H-NMR ($CDCl_3$/TFA) δ: 9.28 (s brad, 1H, NH), 7.39-6.9 (m, 4H, Ar-H), 5.19 (d, 1H, *J* = 10.8 Hz, H_5), 4.15 (t, 1H, H_4), 3.88-3.76 (3s, 9H, 3 x CO_2Me), 3.77 (d, 1H, *J* = 9.9 Hz, H_3), 1.98 (s, 3H, C-Me). Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.09; H, 6.00; N, 3.05.

3,4-Dicyano-2-methyl-5-(4-oxo-4*H*-chromen-3-yl)pyrrolidine-2-carboxylic acid (21) and its isomer (22). The reaction was conducted according to the general procedure (method B) using 3-formylchromone **1c**, DL-alanine **2a** and fumaronitrile **13** to give a 61% total yield of an isomeric mixture of the cycloadducts **21** and **22** in 4.5: 1 ratio, respectively. Fractional crystallization from aqueous methanol (MeOH/H_2O, 3: 2) afforded the minor isomer **22** in a pure state. The minor isomer **22**, mp 224-226 ºC. IR (KBr): 3450 (broad), 2358, 2255, 1720, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.61 (s, 1H, chromonyl-OCH-), 8.24-7.68 (m, 4H, Ar-H), 5.35 (d, 1H, *J* = 11.7 Hz, H_5), 4.43 (t, 1H, H_4), 4.13 (d, 1H, *J* = 11.46, H_3), 3.89 (s, 3H, MeOH, solvent), and 2.1 (s, 3H, C-Me). MS (*m/z* %): 323 (M-MeOH, 6.6), 251 (100), 211 (93), 198 (47), 172 (58), 120 (42), 114 (36), 104 (33), 91 (38), 77 (40) 63 (58) and 51 (36). The major isomer **21**, The ^{1}H-NMR was recorded from the spectrum of the reaction mixture. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.59 (s, 1H, chromonyl-OCH-), 8.21-7.7 (m, 4H, Ar-H), 5.92 (d, 1H, *J* = 10.5 Hz, H_5), 5.1 (d, 1H, *J* = 10.5, H_3), 4.63 (t, 1H, H_4), 3.97 (s, 3H, MeOH, solvent), and 2.1 (s, 3H, C-Me).

3a-(Ethoxycarbonyl)-2-methyl-4-oxo-3-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[4, 3-*b*]pyrrole-2-carboxylic acid (24a). The reaction was carried out according to the general procedure (method B) using salicylaldehyde **1a**, DL-alanine **2a** and ethyl (2*E*)-2-cyano-3-phenylacrylate **23a** to produce the corresponding tricyclic compound **24a** (0.25 g, 64%), mp 166-168 ºC. IR (KBr): 3736, 3443 (broad), 2933 (broad), 2358, 1747, 1710, 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.57-7.05 (m, 9H, Ar-H), 5.72 (s, 1H, H_{9b}), 4.29 (s, 1H, H_3), 4.27 (q, 2H, CO_2CH_2Me), 2.11 (s, 3H, C-Me) and 1.1 (t, 3H, CO_2CH_2Me). MS (*m/z* %): 374(M-44, 48), 242 (27), 197 (74), 172 (36), 147 (78), 127 (56), 101 (48), 76 (100) and 51 (88). Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54. Found: C, 66.12; H, 5.15; N, 3.33.

3-(4-Chlorophenyl)-3a-(ethoxycarbonyl)-2-methyl-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[4,3-*i*]pyrrole-2-carboxylic acid (24b). According to the general procedure (method B) using salicylaldehyde **1a**, DL-alanine **2a** and ethyl (2*E*)-3-(4-Chlo-rophenyl)-2-cyanoacrylate **23b** to afford **24b** (0.26 g, 61%), mp 176-178 ºC. IR (KBr): 3600-2800 (broad), 2356, 1745, 1705, 1617 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.56-7.08 (m, 8H, Ar-H), 5.73 (s, 1H, H_{9b}), 4.34 (s, 1H, H_3), 4.31 (q, 2H, CO_2CH_2Me), 2.14 (s, 3H, C-Me) and 1.15 (t, 3H, CO_2CH_2Me). MS (*m/z* %): 383 (M-44, 35), 234 (90), 206 (48), 190 (69), 161 (54), 147 (100), 131 (54), 121 (57), 107 (74), 76 (81), 68 (45) and 50 (100). Anal. Calcd for $C_{22}H_{20}NO_6Cl$: C, 61.47; H, 4.69; N, 3.26; Cl, 8.25. Found: C, 60.99; H, 4.66 ; N, 3,13; Cl, 8.00.

3a-(Ethoxycarbonyl)-2-methyl-3-(4-nitrophenyl)-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole-2-carboxylic acid (24c). Applying the general procedure (method B) using salicylaldehyde **1a**, DL-alanine **2a** and ethyl (2*E*)-2-cyano-3-(4-nitrophenyl)acrylate **23c** gave **24c** (0.31 g, 71%), mp 160-162 ºC. IR (KBr): 3500-2300 (broad), 2357, 1748, 1710, 1616 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.43-7.11 (m, 8H, Ar-H), 5.78 (s, 1H, H_{9b}), 4.57 (s, 1H, H_3), 4.31 (q, 2H, CO_2CH_2Me), 2.19 (s, 3H, C-Me) and 1.15 (t, 3H, CO_2CH_2Me). MS (*m/z* %): 395 (M-45, 30), 246 (22), 218 (32), 193 (42), 148 (100), 131 (52), 103 (16), 77 (48) and 51 (54). Anal. Calcd for $C_{22}H_{20}N_2O_8$: C, 60.00; H, 4.58; N, 6.36. Found: C, 59.45; H, 4.43; N, 6.28.

3a-(Ethoxycarbonyl)-3-(4-methoxyphenyl)-2-methyl-4-oxo-1,2,3,3a,4,9b-hexahydro-chromeno[4,3-*b*]pyrrole-2-carboxylic acid (24d). According to the general procedure (method B) using salicylaldehyde **1a**, DL-alanine **2a** and ethyl (2*E*)-2-cyano-3-(4-methoxyphenyl)acrylate **23d** formed **24d** (0.2 g, 47%), mp 166-168 ºC. IR (KBr): 3737, 3442-2500 (broad), 2360, 1748, 1710, 1644 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.56-7.10 (m, 8H, Ar-H), 5.72 (s, 1H, H_{9b}), 4.31 (s, 1H, H_3), 4.30 (q, 2H, CO_2CH_2Me), 4.00 (s, 3H, O-Me), 2.14 (s, 3H, C-Me) and 1.16 (t, 3H, CO_2CH_2Me). MS (*m/z* %): 380 (M-45, 100), 273 (40), 227 (97), 186 (34), 148 (56), 131 (26), 107 (33), 77 (61) and 51 (26). Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.62; H, 5.35; N, 3.22.

3a-(Ethoxycarbonyl)-2-methyl-4-oxo-3-spiro(3-indolyl-2-one)-1,2,3,3a,4,9b-hexa-hydrochromeno[4,3-*b*]pyrrole-2-carboxylic acid (24e) and 4-Cyano-4-(ethoxycarbonyl)-5-(2-hydroxyphenyl)-2-methyl-3-spiro-(3-indolyl-2-one)-pyrrolidine-2-carboxylic acid (25e). According to the general procedure (method B) using salicylaldehyde **1a**, DL-alanine **2a** and ethyl *(2E)*-cyano-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetate **23e** gave an inseparable isomeric mixture of the cycloadducts **24e** and **25e** in a 4.5: 1 ratio (0.23 g, 53% total yield), mp 148-150 ºC. IR (KBr): 3737, 3400 (broad), 2357, 1741, 1700, 1630 cm^{-1}. MS (*m/z* %): 261 (M-131-44, 39), 244 (41), 175 (35), 171 (42), 157 (35), 148 (65.7), 145 (100), 129 (47), 118 (42), 89 (39), 77 (57), and 51 (45). The ^{1}H-NMR data for the isomers **24e** and **25e** was recorded from the spectrum of the reaction mixture. The major spiroadduct **24e**. ^{1}H-NMR ($CDCl_3$/TFA) δ: 9.34 (s, 1H, NH), 7.95-7.03 (m, 8H, Ar-H), 6.44 (s, 1H, H_{9b}), 4.19 (2q, 1H, H_A, -OCH_2Me), 4.10 (2q, 1H, H_B, -OCH_2Me), 4.02 (s, 3H, MeOH, solvent), 2.51 (s, 3H, C-Me), 0.96 (t, 3H, -OCH_2Me). The minor spiroadduct **25e**. ^{1}H-NMR ($CDCl_3$/TFA) δ: 9.58 (s, 1H, NH), 7.95-7.03 (m, 8H, Ar-H), 6.35 (s, 1H, H_5), 4.50 (2q, 1H, H_A, -OCH_2Me), 4.30 (2q, 1H, H_B, -OCH_2Me), 2.13 (s, 3H, C-Me), 1.22 (t, 3H, -OCH_2Me).

2-Benzyl-3a-(ethoxycarbonyl)-4-oxo-3-spiro(3-indolyl-2-one)-1,2,3,3a,4,9b-hexahydrochromeno [4,3-*b*]pyrrole-2-carboxylic acid (24f). Conducting the reaction according to the general procedure (method B) using salicylaldehyde **1a**, D-phenylalanine **2d** and ethyl *(2E)*-cyano-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetate **23f** afforded **24f** (0.24 g, 47%), mp 202-204 ºC. IR (KBr): 3737, 3253-2631 (broad), 2361, 1749, 1715, 1689, 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 9.51 (s, 1H, NH), 8.14-7.12 (m, 13H, Ar-H), 6.58 (s, 1H, H_{9b}), 4.30 (d, 1H, *J* = 14.1 Hz, H_A, C-CH_2Ph), 4.25 (2q, 1H, H_C, -OCH_2Me), 4.14 (2q, 1H, H_D, -OCH_2Me), 3.92 (d, 1H, *J* = 14.1 Hz, H_B, C-CH_2Ph), and 1.01 (t, 3H, -OCH_2Me). Anal. Calcd for $C_{29}H_{24}N_2O_7$: C, 67.96; H, 4.72; N, 5.47. Found: C, 67.66; H, 4,47; N, 5.34.

2-Hydroxymethyl-4-(2-hydroxyphenyl)-6,8-dioxo-7-phenyl-3,7-diazabicyclo[3.3.0] octane-2-carboxylic acid (27). According to the general procedure (method A) using salicylaldehyde **1a** as a carbonyl component, DL-serine **2g** as α-amino acid and *N*-phenylmaleimide **26** as a dipolarophile, the *endo*-adduct **27** was obtained after 10 hours in a (0.31 g, 80%). However, using mixed solvent (methanol/toluene, 1: 1) containing a few drops of AcOH afforded a better yield of the *endo*-adduct **27** (0.33g, 86%) after 2 hours. Colourless crystals from aqueous methanol, mp 238-240 ºC. IR (KBr) 3500, 3000 (broad), 2361, 1785, 1710, and 1650 cm^{-1}. 1H-

NMR (DMSO-d_6) δ: 7.46 – 6.68 (m, 9H, Ar-H), 4.89 (d, 1H, J = 9.3 Hz, H_4), 3.84 (d, 1H, J = 11.1 Hz, H_A, -CH_2OH), 3.71 (t, 1H, H_5), 3.74 (d, 1H, J = 11.7 Hz, H_B, -CH_2OH), and 3.46 (d, 1H, J = 7.8 Hz, H_1). MS (*m/z* %): 351 (M-31, 69), 336 (M-45, 22), 320 (73), 186 (60), 160 (100), 132 (92), 120 (60), 93 (82), 77 (87) and 52 (78). Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.80; H, 4.76; N, 7.31.

4-(2-Hydroxyphenyl)-2-(1*H*-imidazol-4-ylmethyl)-6,8-dioxo-7-phenyl-3,7-diaza-bicyclo[3.3.0]octane-2-carboxylic acid (29a). According to the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, L-histidine **2f** (R^1 = CH_2(4-imidazolyl)) as α-amino acid and *N*-phenylmaleimide **26** as a dipolarophile, compound **29a** was obtained after 3 hours as white powder. Crystallization from aqueous methanol gave colorless crystals in (0.17 g, 79%), mp 210-212 ºC. IR (KBr) 3821, 3618, 3472-3155 (broad), 2356, 1701, and 1616 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.68 and 7.77 (2s, 2H, imidazolyl-H), 7.53-6.93 (m, 9H, Ar-H), 5.72 (d, 1H, J = 10.5 Hz, H_4), 4.55 (t, 1H, H_5), 4.16 (d, 1H, J = 9 Hz, H_1), 4.01(s, 2H, C-CH_2-imidazolyl). MS (*m/z* %): 415 (M - 17, 3), 398 (M-34, 36), 350 (16), 159 (17), 131 (14), 93 (100), 83 (37), 77 (42), 66 (33) and 51 (36). Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.86; H, 4.64; N, 12.98.

4-(2-Hydroxy-1-naphthyl)-2-methyl-6,8-dioxo-7-phenyl-3,7-diazabicyclo[3.3.0]octane -2-carboxylic acid (29b). Conducting the general procedure (method A) using 2-hydroxy-1-naphthaldehyde **1b** as carbonyl component, DL-alanine **2a** (R^1 = Me) as α-amino acid and *N*-phenylmaleimide **26** as a dipolarophile, the *endo*-adduct **29b** was obtained after 6 hours as white powder, crystallization from aqueous methanol gave colorless needles (0.395 g, 95%), m.p. 208-210 ºC. IR (KBr) 3737, 3440 (broad), 2357, 1780, 1710, and 1637 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.16-6.90 (m, 11H, Ar-H), 5.65 (d, 1H, J = 7.8 Hz, H_4), 4.10 (t, 1H, H_5), 3.59 (d, 1H, J = 8.1 Hz, H_1), 1.65 (s, 3H, C-Me). MS (*m/z* %) 382 (M–18-16, 40), 381 (100), 233 (44), 206 (38), 182 (35), 144 (41), 115 (41) and 51 (21). Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.00; H, 4.86; N, 6.71.

2-Methyl-6,8-dioxo-4-(4-oxo-4*H*-chromen-3-yl)-7-phenyl-3,7-diazabicyclo[3.3.0]-octane-2-carboxylic acid (29c). The reaction was carried out according to the general procedure (method A) using 3-formylchromone **1c** as carbonyl component, DL-alanine **2a** (R^1 = Me) as α-amino acid and *N*-phenylmaleimide **26** as a dipolarophile, the corresponding compound **29c** was obtained after 30 minutes as white powder. Crystallization from aqueous methanol as a colorless fine needles (0.3 g, 72%), m.p. 280-282 ºC. IR (KBr) 3471 (broad), 2355, 1741, and 1621 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.54 (s, 1H, chromonyl, -OCH-), 8.21-7.24 (m, 9H, Ar-H), 5.86 (d, 1H, J = 10.2 Hz, H_4), 4.40 (t, 1H, H_5), 4.14 (d, 1H, J = 9 Hz, H_1), and 2.10 (s, 3H, C-Me). MS (*m/z* %) 418 (M^+, 53), 373 (M-45, 100), 252 (38), 214 (89), 199 (59), 172 (35), 121 (33), 104 (33), 91 (35), 77 (57), 64 (36) and 51 (32). Anal. Calcd for $C_{23}H_{18}N_2O_6$: C, 66.02; H, 4.34; N, 6.70. Found: C, 66.22; H, 4.31; N, 6.72.

6,8-Dioxo-4-(4-oxo-4*H*-chromen-3-yl)-7-phenyl-3,7-diazabicyclo[3.3.0]octane-2-carboxylic acid (29d). According to the general procedure (method A) using 3-formylchromone **1c** as carbonyl component, glycine **2** (R^1 = H) as α-amino acid and *N*-phenylmaleimide **28** as a

dipolarophile, compound **29d** was obtained after 30 minutes as white amorphous, crystallization from aqueous methanol as a colorless fine needles (0.339 g, 84%), m.p. 266-268 ºC. IR (KBr) 3736, 3450-3236 (broad), 2356, 1713, and 1621 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.3 (s, 1H, chromonyl, -OCH-), 8.10 – 7.15 (m, 9H, Ar-H), 4.38 (d, 1H, *J* = 7.8 Hz, H_4), 3.98 (d, 1H, *J* = 6.9 Hz, H_2), 3.77 (t, 1H, H_5), 3.69 (t, 1H, H_1). MS (*m/z* %) 404(M^+, 22), 359 (M-45, 36), 255 (27), 237 (51), 211 (100), 184 (86), 162 (61), 103 (36), 90 (45), 76 (56), 64 (56) and 51 (44). Anal. Calcd for $C_{22}H_{16}N_2O_6$: C, 65.34; H, 3.99; N, 6.93. Found: C, 65.31; H, 4.00; N, 6.90.

2-{[(2-Amino-2-carboxyethyl)dithio]methyl}-6,8-dioxo-4-(4-oxo-4*H*-chromen-3-yl)-7-phenyl-3,7-diazabicyclo[3.3.0]octane-2-carboxylic acid (29e). According to the general procedure (method A) using 3-formylchromone **1c** as carbonyl component, L-cysteine **2** (R^1 = CH_2SH) as α-amino acid and *N*-phenylmaleimide **26** as a dipolarophile, gave after 2 hours a (0.239 g, 42%) of the corresponding *endo*-cycloadduct **29e**. Compound **29e** was obtained authentically in a 49% yield after 20 hours according to the general procedure (method A) using L-cystine **2** (R^1 = $CH_2SSCH_2CH(NH_2)COOH$) as α-amino acid. Colourless crystals from methanol, mp 256-258 ºC. IR (KBr) 3736, 3446 (broad), 1780, 1710, and 1636 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.49 (s, 1H, chromonyl, -OCH-), 8.20-7.19 (m, 9H, Ar-H) 5.82 (d, 1H, *J* = 10.2 Hz, H_4), 4.54-4.34 (m, 3H, H_5 + -SCH_2CH- + H_1), 4.4 (d, 1H, *J* = 15.30 Hz, H_A, -CH_2S-), 3.9 (d, 1H, *J* = 15.9 Hz, H_B, -CH_2S-), 3.7(dd,1H, *J* = 9.90 and 19.50 Hz, H_A, -SCH_2-) and 2.9 (dd, 1H, *J* = 5.40 and 19.20 Hz, H_B, -SCH_2-). MS (*m/z* %): 373 (M-152- 44, 11), 371 (46), 277 (13), 251 (36), 206 (33), 173 (95), 172 (100), 119 (52), 104 (34), 90 (36), 76 (44), 63(61) and 50 (67). Anal. Calcd for $C_{26}H_{23}N_3O_8S_2$: C, 54.82; H, 4.07; N, 7.38; S, 11.26. Found: C, 54.80; H, 4.00; N, 7.20; S, 11.27.

2-(2-Hydroxyphenyl)-1,3-thiazolidine-4-carboxylic acid (30) and (31). According to the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, L-cysteine **2h** as α-amino acid and *N*-phenylmaleimide **26** as a dipolarophile. An isomeric mixture of the corresponding cyclization products **30** and **31** was obtained after 15 minutes in a 1.5: 1 ratio, respectively in almost quantitative yield (0.22 g, 98%) and the unreacted *N*-phenylmaleimide **26** was recovered. Crystallization from aqueous methanol as a colourless crystals, mp 160–162 ºC. IR (KBr) 3737, 3437 (broad), 3100, 2364, 1623 cm^{-1}: MS (*m/z* %): 225 (M^+, 40), 180 (M-45, 13), 153 (48), 137 (53), 132 (99), 120 (37), 91 (40), 77 (100), 65 (39) and 51 (88). Due to solubility difficulties many attempts failed to give the two isomers **30** and **31** in pure states, and the spectral data was assigned for the crude reaction mixture. The major isomer **30**: ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.69-6.93 (m, 4H, Ar-H), 6.12 (s, 1H, H_2), 5.1 (dd, 1H, *J* = 6.3 and 7.2 Hz, H_4), 3.81 (dd, 1H, *J* = 8.4 and 8.1 Hz, H_A, CH_2S), and 3.67 (dd, 1H, *J* = 5.7 Hz, H_B, CH_2S). The minor isomer **(31):** ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.69-6.93 (m, 4H, Ar-H), 6.20 (s, 1H, H_2), 5.15 (t, 1H, H_4), 3.89 (d, 1H, *J* = 7.5 Hz, H_A, CH_2S), and 3.85 (d, 1H, *J* = 7.5 Hz, H_B, CH_2S).

Methyl-4-(2-hydroxyphenyl)-2-methyl-6,8-dioxo-7-phenyl-3,7-diazabicyclo[3.3.0]-octane-2-carboxylate (33). In tow nicked flask containing dry methanol (20 ml) was added the acid **32** (0.37 g, 0.001 mol) and then dry HCl gas was passed through the reaction mixture for 1 hour,

and finally the solution was refluxed for 5 hours. The reaction mixture was allowed to reach to room temperature and the solvent was removed under reduced pressure. The formed amino ester hydrochloride was dissolved in methylene chloride and neutralized by sodium bicarbonate solution (5%). The organic layer was separated and washed with water and saturated sodium chloride solution then dried over $MgSO_4$. the solvent was evaporated under reduced pressure to afford nearly a quantitative yield (0.38 g, 100%) of the corresponding ester **33**. Colourless needles (CH_2Cl_2/pet-ether 40-60), m.p. 190-192 ºC. IR (KBr) 3550, 3350, 1780, 1740, and 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.45-6.84 (m, 9H, Ar-H), 4.99 (d, 1H, J = 9.9 Hz, H_4), 3.83 (s, 3H, CO_2Me), 3.72 (t, 1H, H_5), 3.48 (d, 1H, J = 8.1 Hz, H_1), 1.73 (s, 3H, C-Me), and 1.57 (s broad, 1H, NH). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.3; H, 5.3; N, 7.37. Found: C, 65.30; H, 4.99; N, 7.20.

Methyl 3-(anilinocarbonothioyl)-4-(2-hydroxyphenyl)-2-methyl-6,8-dioxo-7-phenyl-3,7-diazabicyclo[3.3.0]octane-2-carboxylate (35). An equimolar mixture of the ester **33** (0.38 g, 0.001 mol) and phenylisothiocyanate **34** (0.12 ml, 0.001 mol) in methanol (5 ml) in the presence of catalytic amount of HCl, was stirred at room temperature for 10 minutes, by which time the reactants went into the solution and a white precipitate came out of solution on cold. The obtained thiourea derivative **35** was filtered off as off-white solid (0.5 g, 97%), crystallized from (CH_2Cl_2/pet-ether 40-60) as a colourless crystals, m.p. 230-232 ºC. IR (KBr) 3650, 1790, 1770, and 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.54-6.90 (m, 14H, Ar-H), 5.75 (d broad, 1H, H_4), 4.54 (t broad, 1H, H_5), 4.10 (s, 3H, MeOH, solvent), 4.08 (d, 1H, H_1), 4.06 (s, 3H, CO_2Me), 2.18 (s, 3H, C-Me). Anal. Calcd for $C_{28}H_{25}N_3O_5S$: C, 65.22; H, 4.89; N, 8.15; S, 6.22. Found: C, 64.58; H, 4.65; N, 7.99; S, 6.09.

5-(2-hydroxyphenyl)-8b-methyl-2,7-diphenyl-3-thioxohexahydropyrrolo[3',4':3,4]-pyrrolo[1,2-*c*]imidazole-1,6,8(7*H*)-trione (36). Stirring the thiourea derivative **35** (0.52 g, 0.001 mol) in pyridine (5 ml) at room temperature for 24 hour, and the solvent was evaporated under vacuum to give (0.458 g, 95%) of the corresponding thiohydantoin **36**. However the thiohydantoin **36** was obtained by stirring a mixture of the amino ester **33** (0.38 g, 0.001 mol) and phenylisothiocyanate **34** (0.12 ml, 0.001 mol) in pyridine (5 ml) at room temperature for 24 hours. Removing the solvent under reduced pressure afforded (0.473 g, 98%) of the corresponding thiohydantoin derivative **36**. Crystallization from (CH_2Cl_2/pet-ether 40-60) to give colourless crystals, m.p. 294-296 ºC. IR (KBr) 3600-3500 (broad), 1790, 1750, and 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 8.88-8.12 (m, 5H, pyridine), 7.53-6.81 (m, 14H, Ar-H), 5.84 (d, 1H, H_5), 4.84(t, 1H, H_{5a}), 4.23 (d, 1H, J = 8.4 Hz, H_{8a}), 2.12 (s, 3H, C-Me). MS (*m/z* %) 483 (M^+, 47), 450 (21), 319 (44), 278 (19), 172 (49), 146 (18), 130 (26), 92 (100), 76 (83) and 50 (30). Anal. Calcd for $C_{27}H_{21}N_3O_4S$ requires C, 67.06; H, 4.38; N, 8.69; S, 6.63. Found: C, 66.58; H, 4.08; N, 8.28; S, 6.39.

5-(2-hydroxyphenyl)-2-methyl-4-nitro-3-phenylpyrrolidine-2-carboxylic acid (44a). The cycloadduct **44a** was obtained in a (0.181 g, 53%) after 3 hours according to the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, DL-alanine **2a** as α-amino acid and β-nitrostyrene **43** (Ar^1 = Ph) as a dipolarophile. Colourless crystals from aqueous

methanol, mp 204-206 ºC. IR (KBr) 3600-2943 (broad), 2356, and 1617 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.54-6.80 (m, 9H, Ar-H), 5.29 (t, 1H, H_4), 5.04 (d, 1H, J = 8.1 Hz, H_5), 4.32 (d, 1H, J = 7.8 Hz, H_3) and 0.95 (s, 3H, C-Me). MS (*m/z* %): 342 (M^+, 18), 297 (M-45, 30), 250 (87), 210 (100), 146 (33), 115 (29), 91 (34), 77 (27) and 51 (21). Stereochemistry was assigned based on NOE difference spectroscopy (DMSO-d_6, 300MHz). Thus irradiation of 3-H affect enhancements in 4-H (1.70%), 5-H (3.35%), 2-Me (0.50%) and Ar (8.83% at δ = 7.65 ppm), whilst irradiation of 4-H resulted in enhancement of 3-H (1.70%) and Ar (9.75% at δ = 7.30 ppm and 2.86% at δ = 7.65 ppm). Irradiation of 5-H caused enhancement in 3-H (3.23%) and Ar (3.81% at δ = 7.65 ppm). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.16; H, 5.30; N, 8.18. Found: C, 63.19; H, 5.10; N, 8.21.

2-benzyl-5-(2-hydroxyphenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylic acid (44b). The reaction was conducted according to the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, D-phenylalanine **2b** as α-amino acid and β-nitrostyrene **43** (Ar^1 = Ph) as a dipolarophile to afford the adduct **44b** in a (0.238 g, 57%) after 5 h. Colourless crystals from aqueous methanol, mp 216-218 ºC. IR (KBr) 3736, 3443 (broad), 2300, and 1616 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.62-7.10 (m, 14H, Ar-H), 6.28 (t, 1H, H_4), 5.46 (d, 1H, J = 10.2 Hz, H_5), 4.79 (d, 1H, J = 10.2 Hz, H_3) and 3.11 (s, 2H, C-CH_2Ph). MS (*m/z* %): 340 (M-77-1, 29), 220 (30), 173 (25), 132 (25), 117 (36), 104 (35), 90 (97), 77 (100) and 51 (80). Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.88; H, 5.30; N, 6.70. Found: C, 68.85; H, 5.33; N, 6.73.

5-(2-hydroxyphenyl)-2-isobutyl-4-nitro-3-phenylpyrrolidine-2-carboxylic acid (44c). Application of the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, L-leucine **2c** as α-amino acid and β-nitrostyrene **43** (Ar^1 = Ph) as a dipolarophile. The cycloadduct **44c** was obtained after 4 hours as a white powder. Crystallization from aqueous methanol gave colourless crystals in a (0.169 g, 44%), mp 200-202 ºC. IR (KBr) 3448-3146 (broad), 2350, and 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.52-6.99 (m, 9H, Ar-H), 6.11 (t, 1H, H_4), 5.47 (d, 1H, J = 10.5 Hz, H_5), 4.60 (d, 1H, J = 10.5 Hz, H_3), 1.93 (dd, 1H, J = 4.2 and 15.0 Hz, H_A, C-CH_2CHMe$_2$), 1.76 (m, 1H, -CH_2CHMe$_2$), 1.59 (dd, 1H, J = 8.1 and 15.0 HZ, H_B, C-CH_2CHMe$_2$), 0.93 (d, 3H, J = 6.6 Hz, CHMe$_A$) and 0.82 (d, 3H, J = 6.3 Hz, CHMe$_B$). MS (*m/z* %): 384 (M^+, 11), 339 (M-45, 15), 292 (42), 236 (15), 209 (100), 131 (17), 115 (24), 91 (28), 77 (20) and 51 (12). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.58; H, 6.32; N, 7.26.

5-(2-hydroxyphenyl)-2-[2-(methylthio)ethyl]-4-nitro-3-phenylpyrrolidine-2-carboxylic acid (44d). The reaction was carried out According to the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, DL-methionine **2d** as α-amino acid and β-nitrostyrene **43** (Ar^1 = Ph) as a dipolarophile. The cycloadduct **44d** was obtained after 4 hours as white amorphous. Colourless crystals was obtained from aqueous methanol in a (0.177 g, 44%), mp 204-206 ºC. IR (KBr) 3438-3136 (broad), 2350, and 1616 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.56-7.06 (m, 9H, Ar-H), 6.24 (t, 1H, H_4), 5.55 (d, 1H, J = 10.5 Hz, H_5), 4.71 (d, 1H, J = 10.5 Hz, H_3), 2.62 (t, 2H, CH_2CH_2S), 2.28 (dd, 1H, J = 7.8 and 15.3 Hz, H_A, CH_2CH_2S), 2.08 (dd, 1H, J = 6.6 and 15.6 Hz, H_B, CH_2CH_2S), 2.04 (s, 3H, SMe). MS (*m/z* %): 402 (M^+, 7), 357 (M-45, 36), 310

(38), 281 (24), 262 (59), 209 (100), 131 (22), 115 (28), 75 (45) and 51 (16). Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.68; H, 5.51; N, 6.96; S, 7.97. Found: C, 59.70; H, 5.53; N, 6.93; S, 7.99.

3-(2-furyl)-5-(2-hydroxyphenyl)-2-methyl-4-nitropyrrolidine-2-carboxylic acid (46e). Application of the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, DL-alanine **2a** as α-amino acid and 2-[(*E*)-2-nitrovinyl]furan **43** (Ar^1 = furyl) as a dipolarophile, the corresponding compound **44e** was obtained after 5 hours. Crystallization from aqueous methanol yielded (0.15 g, 45%), mp 198-200 ºC. IR (KBr) 3467-3100 (broad), 2361, and 1617 cm^{-1}: ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.58-6.53 (m, 7H, Ar-H), 6.19 (t, 1H, H_4), 5.54 (d, 1H, J = 9.6 Hz, H_5), 4.79 (d, 1H, J = 9.0 Hz, H_1) and 1.76 (s, 3H, C-Me). MS (*m/z* %): 332 (M^+, 5), 239 (15), 198 (100), 148 (21), 130 (26), 120 (19), 91 (16), 77 (32) and 50 (35). Stereochemistry was assigned by NOE difference spectroscopy (DMSO-d_6, 300MHz). Irradiation of 3-H affect enhancements in the signals for 4-H (1.43%), 5-H (2.50%), 2-Me (0.75%) and Ar (1.94% at δ = 6.45 ppm), whilst irradiation of 4-H resulted in enhancement of 3-H (1.34%), 2-Me (1.18%) and Ar (3.84% at δ = 6.45 ppm and 2.52% at δ = 7.45 ppm). Irradiation of 5-H caused enhancement in 3-H (4.00%), 2-Me (0.22%) and Ar (0.22% at δ = 7.45 ppm). Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.85; H, 4.83; N, 8.40.

2-benzyl-3-(2-furyl)-5-(2-hydroxyphenyl)-4-nitropyrrolidine-2-carboxylic acid (44f). The reaction was carried out according to the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, D-phenylalanine **2b** as α-amino acid and 2-[(*E*)-2-nitrovinyl]furan **43** (Ar^1 = furyl) as a dipolarophile to afford the cycloadduct **44f** after 5 hours as white amorphous in a (0.122 g, 30%). Crystallization from aqueous methanol gave colourless crystals, mp 196-198 ºC. IR (KBr) 3600-3109 (broad), 2350, and 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.64-6.55 (m, 12H, Ar-H), 6.17 (t, 1H, H_4), 5.42 (d, 1H, J = 10.5 Hz, H_5), 4.85 (d, 1H, J = 9 Hz, H_3) and 3.26 (q, 2H, C-CH_2Ph). MS (*m/z* %): 408 (M^+, 4), 363 (M-45, 3), 317(11), 270 (12), 225 (16), 199 (100), 131 (15), 91 (48), 77 (14), 65 (18) and 51 (11). ^{13}C-NMR (DMSO-d_6) 175.12, 155.52, 149.46, 143.45, 135.99, 129.61, 128.97, 128.00, 127.53, 126.59, 124.21, 119.13, 115.17, 110.78, 109.86, 92.44, 69.95, 60.06, 50.62, 41.96. Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.93; N, 6.86. Found: C, 64.72; H, 4.96; N, 6.89.

3-(2-furyl)-5-(2-hydroxyphenyl)-2-[2-(methylthio)ethyl]-4-nitropyrrolidine-2-carboxylic acid (44g). The mixture was carried out according to the general procedure (method A) using salicylaldehyde **1a** as carbonyl component, DL-methionine **2d** as α-amino acid and 2-[(*E*)-2-nitrovinyl]furan **43** (Ar^1 = furyl) as dipolarophile, the corresponding adduct **44g** was obtained after 3 hours (0.129 g, 33%). Crystallization from aqueous methanol, mp 210-212 ºC. IR (KBr) 3735, 3600-3133 (broad), 2353, and 1618 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TFA) δ: 7.59-6.53 (m, 7H, Ar-H), 6.18 (t, 1H, H_4), 5.56 (d, 1H, J = 10.2 Hz, H_5), 4.83 (d, 1H, J = 9.3 Hz, H_3), 2.65 (m, 2H, -CH_2CH_2S), 2.38-2.27 (2m, 2H, C-CH_2CH_2S), 2.08 (s, 3H, -SMe). Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14; S, 8.17. Found: C, 55.10; H, 5.17; N, 7.16; S, 8.15.

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