Stereospecific non-decarboxylative 1,3-dipolar cycloaddition as a potential route to proline derivatives, part III¹

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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).

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, THF, THF/H\(_2\)O, MeCN/H\(_2\)O (Table 2, entries 6-9). The observed modest yields are mainly due to solubility problems in THF, THF/H\(_2\)O, MeCN/H\(_2\)O and the harsh conditions in the case of AcOH.

\[
\begin{align*}
\text{Ar} & \equiv \text{O} + \text{H}_2\text{N} \text{CO}_2\text{H} \xrightarrow{\text{MeOII/H}^+ \text{reflux 2h}} \text{Ar} \equiv \text{N} \text{CO}_2\text{H} \\
& \xrightarrow{\text{stereomutation}} \text{H} \equiv \text{N} \text{CO}_2\text{H} \\
\text{(syn-dipole)} & 6 \quad \text{(anti-dipole)} 7 \\
\text{MeO}_2\text{C} & \equiv \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} & \equiv \text{CO}_2\text{Me} \\
4a & + 4b + 4c \\
\text{Ar} & = 2\text{HOC}_{3}\text{H}_4^-
\end{align*}
\]

Scheme 2
Table 1. The effect of solvent and temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent(^a)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio, 4a: 4b: 4c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH(^b)</td>
<td>48</td>
<td>39</td>
<td>46: 54: 0</td>
</tr>
<tr>
<td>2</td>
<td>MeOH(^c)</td>
<td>48</td>
<td>98</td>
<td>41: 47: 12</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>2</td>
<td>66</td>
<td>50: 40: 10</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>2</td>
<td>56</td>
<td>57: 29: 14</td>
</tr>
<tr>
<td>5</td>
<td>(^n)PrOH</td>
<td>2</td>
<td>64</td>
<td>100: 0: 0</td>
</tr>
<tr>
<td>6</td>
<td>AcOH(^d)</td>
<td>1</td>
<td>38</td>
<td>100: 0: 0</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>18</td>
<td>37</td>
<td>100: 0: 0</td>
</tr>
<tr>
<td>8</td>
<td>THF/H(_2)O</td>
<td>18</td>
<td>27</td>
<td>100: 0: 0</td>
</tr>
<tr>
<td>9</td>
<td>MeCN/H(_2)O</td>
<td>18</td>
<td>39</td>
<td>100: 0: 0</td>
</tr>
</tbody>
</table>

\(^a\)The reaction was conducted in boiling solvent. \(^b\)The reaction was conducted at 0 °C. \(^c\)The reaction was conducted at 30 °C.

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\(^\text{10}\) 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

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>d, H(_3)</th>
<th>t, H(_4)</th>
<th>d, H(_5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>J(_{3,4}) (Hz)</td>
<td>J(<em>{3,4}, J</em>{4,5}) (Hz)</td>
<td>J(_{3,4}) (Hz)</td>
</tr>
<tr>
<td>4a</td>
<td>9</td>
<td>9.3, 10.8</td>
<td>10.8</td>
</tr>
<tr>
<td>10b</td>
<td>9</td>
<td>9, 10.8</td>
<td>10.5</td>
</tr>
<tr>
<td>10c</td>
<td>9.6</td>
<td>9.6, 10.2</td>
<td>10.8</td>
</tr>
</tbody>
</table>
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
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 $^1\text{H}$-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 imidazolyl nitrogen atom would serve as an excellent candidate for the stabilizing bifocal hydrogen bonding.

Ar = 2-HOC$_6$H$_4$, R = -CH$_2$(4-imidazoly), (43%)
Table 3. $^1$H NMR data for 16a-f

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>d, H$_3$ $\delta$ (ppm)</th>
<th>J$_{3,3a}$ (Hz)</th>
<th>H$_{3a}$ $\delta$ (ppm)</th>
<th>J$<em>{3,3a}$, J$</em>{3a,3b}$ (Hz)</th>
<th>d, H$_{9b}$ $\delta$ (ppm)</th>
<th>J$_{3a,9b}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16a</td>
<td>3.96</td>
<td>11.7</td>
<td>4.44</td>
<td>t</td>
<td>5.29</td>
<td>11.4</td>
</tr>
<tr>
<td>16b</td>
<td>4.05</td>
<td>11.7</td>
<td>4.33</td>
<td>t</td>
<td>4.59</td>
<td>11.7</td>
</tr>
<tr>
<td>16c</td>
<td>3.97</td>
<td>11.7</td>
<td>4.39</td>
<td>t</td>
<td>5.30</td>
<td>12.0</td>
</tr>
<tr>
<td>16d</td>
<td>3.95</td>
<td>9.3</td>
<td>4.42</td>
<td>dd (9.0, 11.4)</td>
<td>5.17</td>
<td>11.7</td>
</tr>
<tr>
<td>16e</td>
<td>4.25</td>
<td>11.1</td>
<td>4.41</td>
<td>t</td>
<td>4.73</td>
<td>11.7</td>
</tr>
<tr>
<td>16f</td>
<td>4.83</td>
<td>6.0</td>
<td>4.39</td>
<td>dd (6.3, 8.1)</td>
<td>5.66</td>
<td>8.4</td>
</tr>
</tbody>
</table>

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. 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-$\alpha$-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.
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-3H-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 $\delta = 4.50$ and 4.30 ppm, whilst the ethyl ester methylene protons at C-3a of the major isomer 24e appeared as two double quartets at $\delta = 4.19$ 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 $\delta = 4.25$ and 4.14 ppm for the C-3a ethyl ester methylene protons. The stereochemistry of the obtained adducts was confirmed by their spectral data.

**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-3H-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 $\delta = 4.50$ and 4.30 ppm, whilst the ethyl ester methylene protons at C-3a of the major isomer 24e appeared as two double quartets at $\delta = 4.19$ 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 $\delta = 4.25$ and 4.14 ppm for the C-3a ethyl ester methylene protons. The stereochemistry of the obtained adducts was confirmed by their spectral data.
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). 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).

\[
\text{Ar} = 2\text{-HOC}_{6}\text{H}_{4}^+, \\
\begin{align*}
\text{Conditions:} & \quad \text{(a)} \quad \text{AcOH, 100°C, 15min, 8:3, unreported yield.} \\
& \quad \text{(b)} \quad \text{MeOH/H}^+, \text{reflux 10h, 100:0, 80%.} \\
& \quad \text{(c)} \quad \text{MeOH/Toluene + drops of AcOH (1:1), reflux 2h, 100:0, 86%}. \\
\end{align*}
\]

\textbf{Scheme 9}

It was reported that the Schiff bases of a histidine tethered resin reacted with \textit{N}-substitutedmaleimides to give isomeric mixtures of the corresponding cycloadducts (four isomers) in modest to good yields (31-82%). Using our methodology, salicylaldehyde 1a reacted with L-histidine 2 (R\textsuperscript{1} = CH\textsubscript{2}(4-imidazolyl)) and \textit{N}-phenylmaleimide 26 to give the stereospecific \textit{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. In this case the \textit{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\textsuperscript{1} = Me) and \textit{N}-phenylmaleimide 26 under the same conditions to give a 95% yield of the \textit{endo}-adduct 29b. Similarly, the reaction of 3-formylchromone 1c with both DL-alanine 2 (R\textsuperscript{1} = Me) and glycine 2 (R\textsuperscript{1} = H) in the presence of \textit{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\textsuperscript{1} = CH\textsubscript{2}SH) in the presence of \textit{N}-phenylmaleimide 26 to give a 42% yield of the \textit{endo}-cycloadduct 29e as the only product. The stereochemistry of the stereospecific \textit{endo}-cycloadduct 29e was confirmed authentically, thus reacting 3-formylchromone 1c with L-cysteine 2 (R\textsuperscript{1} = CH\textsubscript{2}SSCH\textsubscript{2}CH(NH\textsubscript{2})COOH) and \textit{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\textsuperscript{1} = CH\textsubscript{2}SH) the cycloaddition occurred first and then the (-CH\textsubscript{2}SH) at C\textsubscript{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.

\[
\text{Ar} = 2\text{-hydroxynaphthyl, } R^1 = R^2 = \text{CH}_2(4\text{-imidazolyl}) (79\%)
\]

\[
a, Ar = 2\text{-hydroxynaphthyl, } R^1 = R^2 = \text{Me} (95\%)
\]

\[
c, Ar = 3\text{-chromonyl, } R^1 = R^2 = \text{Me} (72\%)
\]

\[
d, Ar = 3\text{-chromonyl, } R^1 = R^2 = \text{H} (84\%)
\]

\[
e, Ar = 3\text{-chromonyl, } R^1 = \text{CH}_2\text{SH}, R^2 = \text{CH}_2\text{SSCH}_2\text{CH(NH}_2\text{)}\text{COOH} (42\%)
\]

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. 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.

Scheme 11

It is well known that thiohydantoins containing heterocycles have interesting biological effects. It seems that the ester derivative 33 would serve well in the thiohydantoin synthesis. Boiling the carboxylic acid derivatives 32 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.\textsuperscript{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).\textsuperscript{4,18} Cossio\textsuperscript{19} and others\textsuperscript{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.\textsuperscript{21}

**Scheme 13**
However, in our laboratory, the \( \alpha \)-amino acids 2a-d readily reacted with salicylaldehyde 1a and \( \beta \)-nitrostyrene 43 \((Ar^1 = Ph)\) in boiling acidified methanol to give the stereospecific cycloadducts 44a-d in moderate yields (44-53\%), through the \textit{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.\(^4\) 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-\textit{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.

![Scheme 14](image)

Similarly, \( \alpha \)-amino acids 2 \((R = Me, -CH_2Ph, -CH_2CH_2SMe)\) reacted with salicylaldehyde 1a and 2-\([(E)-2\text{-nitrovinyl}]furan\) 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-\textit{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, \textit{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

<table>
<thead>
<tr>
<th>Entry</th>
<th>$\text{H}_3$</th>
<th>$\text{H}_4$</th>
<th>$\text{H}_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>d, 4.32</td>
<td>7.8</td>
<td>t, 5.29</td>
</tr>
<tr>
<td>b</td>
<td>d, 4.79</td>
<td>10.2</td>
<td>t, 6.28</td>
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<tr>
<td>c</td>
<td>d, 4.60</td>
<td>10.5</td>
<td>t, 6.11</td>
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<td>d</td>
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<tr>
<td>e</td>
<td>d, 4.79</td>
<td>9.0</td>
<td>t, 6.19</td>
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<tr>
<td>f</td>
<td>d, 4.85</td>
<td>9.0</td>
<td>t, 6.17</td>
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<tr>
<td>g</td>
<td>d, 4.83</td>
<td>9.3</td>
<td>t, 6.18</td>
</tr>
</tbody>
</table>

$^1$H-NMR solvent is CDCl$_3$/TFA; * $^1$H-NMR solvent is DMSO-\textit{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 $\delta$ 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 24C 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/H2O, 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/H2O, 3:2). The cycloadducts prepared by this method were heated at 95 °C to get rid of the solvent (MeOH); in some cases we could not remove MeOH completely at this degree, e.g. the cycloadducts 16a-e, 21, 22 and 24e. However, either heating at 95 °C 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 °C. IR (KBr) 3737, 3373 (broad), 2370, 1700 (broad), and 1630 cm⁻¹. ¹H-NMR (CDCl3/TFA) δ: 7.93-7.12 (m, 6H, Ar-H), 6.06 (d, 1H, J = 10.5 Hz, H5), 4.34 (t, 1H, H4), 3.97 (d, 1H, J = 9 Hz, H3), 3.90 and 3.62 (2s, 6H, 2 x CO2Me) and 2.15 (s, 3H, C-Me). Anal. Calcd for C20H21NO7: 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-4H-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 °C. IR (KBr) 3000 (broad), 1740 (broad), and 1635 cm⁻¹. ¹H-NMR (CDCl3/TFA) δ: 8.54 (s, 1H, chromonyl, -OCH-), 8.23-7.68 (m, 4H, Ar-H), 5.25 (d, 1H, J = 10.5 Hz, H5), 4.24 (t, 1H,
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 °C. IR (KBr): 3750, 3446-2657 (broad), 2362, 2250, 1745, 1615 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.15-7.00 (m, 4H, Ar-H), 5.29 (d, 1H, J = 11.4 Hz, H₉β), 4.44 (t, 1H, H₉a), 3.98 (s, 3H, MeOH, solvent), 3.96 (d, 1H, J = 11.7 Hz, H₅) 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). ¹³C-NMR (DMSO-d₆/TFA) 169.74, 167.47, 156.15, 131.50, 129.65, 119.44, 116.27, 115.94, 115.72, 67.95, 58.17, 54.06, 52.75, 34.39, 21.51. DEPT (DMSO-d₆/TFA) 131.52, 129.66, 119.42, 115.72, 58.10, 54.03, 52.76, 34.37, 21.51. Anal. Calcd for C₁₄H₁₂N₂O₄: 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 °C. IR (KBr): 3737, 3609-2947 (broad), 2357, 2250, 1738, 1643 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.48-6.93 (m, 9H, Ar-H), 4.59 (d, 1H, J = 11.7 Hz, H₉β), 4.33 (t, 1H, H₉a), 4.05 (d, 1H, J = 11.7 Hz, H₅), 4.01 (s, 3H, MeOH, solvent), 3.84 (d, 1H, J = 11.3 Hz, H₆A, C-CH₂Ph) and 3.69 (d, 1H, J = 15.0 Hz, H₆B, C-CH₂Ph). MS (m/z %): 275 (M⁺-28), 223 (19), 185 (29), 159 (16), 133 (10), 106 (15), 91 (100), 77 (26), 64 (26) and 51 (22). Anal. Calcd for C₂₀H₁₆N₂O₄: 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 salicylaldeddehyde 1a, L-leucine 2c and fumaronitrile 13 to afford 16c (0.15 g, 43%), mp 204-206 °C. IR (KBr): 3728, 3438-2961 (broad), 2355, 2253, 1730, 1622 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.51-7.00 (m, 4H, Ar-H), 5.3 (d, 1H, J = 12 Hz, H₉β), 4.39 (t, 1H, H₉a), 4.01 (s, 3H, MeOH, solvent), 3.97 (d, 1H, J = 11.7 Hz, H₅), 2.64 (dd, 1H, J = 7.5 and 15.3 Hz, H₆A, C-CH₂CH), 2.37 (dd, 1H, J = 6.0 and 15.3 Hz, H₆B, C-CH₂CH), 1.91 (m, 1H, -CHMe₂), 1.06 and 1.03 (2d, 6H, J 6.6 Hz, -CHMe₂). 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 C₁₇H₁₈N₂O₄: 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 °C. IR (KBr): 3734, 3366-2650 (broad), 2352, 2255, 1734, 1620 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.52-7.02 (m, 4H, Ar-H), 5.17 (d, 1H, J = 11.7 Hz, H₉b), 4.42 (dd, 1H, J = 9 and 11.4, H₃a), 3.96 (s, 3H, MeOH, solvent), 3.95(d, 1H, J = 9.3 Hz, H₃), 2.99-2.66 (m, 4H, C-(CH₂)₂-S-) and 2.23 (s, 3H, -SMe). MS (m/z %): 319 (M⁻, 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 C₁₆H₁₆N₂O₄S.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-(1H-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 °C. IR (KBr): 3737, 3359 (broad), 2357, 2268, 1740, 1630 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.74-6.96 (m, 10H, Ar-H and NH), 4.73 (d, 1H, J = 11.7 Hz, H₉b), 4.41 (t, 1H, H₃a), 4.25 (d, 1H, J = 11.1 Hz, H₃), 4.1 (s, 3H, MeOH, solvent), and 4.05 (d, 2H, J = 3.6 Hz, C-CH₂-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 C₂₂H₁₇N₃O₄.MeOH: C, 65.86; H, 5.05; N, 10.02. Found: C, 65.43; H, 5.00; N, 9.88.

3-Cyano-2-(1H-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 °C. IR (KBr): 3600-2700 (broad), 2350, 2243, 1720, 1600 cm⁻¹. ¹H-NMR (CDCl₃/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, H₃), 4.83 (d, 1H, J = 6.0 Hz, H₉b), 4.39 (dd, 1H, J = 6.3 and 8.1 Hz, H₃a), 4.04 (d, 1H, J = 16.2 Hz, Hₐ, C-CH₂-imidazolyl), 3.90 (d, 1H, J = 15.9 Hz, H₈, C-CH₂-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 C₁₇H₁₄N₄O₄: 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 CH₂Cl₂ (20 mL) and neutralized by aqueous NaHCO₃ (5%). The organic layer was separated and washed by water and saturated sodium chloride solution then dried over MgSO₄. 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 °C (CH₂Cl₂/pet-ether 40-60). ¹H-NMR (CDCl₃/TFA) δ: 9.28 (s broad, 1H, NH), 7.39-6.9 (m, 4H, Ar-H), 5.19 (d, 1H, J = 10.8 Hz, H₃), 4.15 (t, 1H, H₄), 3.88-3.76 (3s, 9H, 3 x CO₂Me), 3.77 (d, 1H, J = 9.9 Hz, H₃), 1.98 (s, 3H, C-Me). Anal. Calcd for C₁₇H₂₁NO₇: 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-4H-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/H2O, 3:2) afforded the minor isomer 22 in a pure state. The minor isomer 22, mp 224-226 °C. IR (KBr): 3450 (broad), 2358, 2255, 1720, 1625 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 8.61 (s, 1H, chromonyl-OCH-), 8.24-7.68 (m, 4H, Ar-H), 5.35 (d, 1H, J = 11.7 Hz, H₃), 4.43 (t, 1H, H₄), 4.13 (d, 1H, J = 11.46, H₃), 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 ¹H-NMR was recorded from the spectrum of the reaction mixture. ¹H-NMR (CDCl₃/TFA) δ: 8.59 (s, 1H, chromonyl-OCH-), 8.21-7.7 (m, 4H, Ar-H), 5.92 (d, 1H, J = 10.5 Hz, H₃), 5.1 (d, 1H, J = 10.5, H₃), 4.63 (t, 1H, H₄), 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 (2E)-2-cyano-3-phenylacrylate 23a to produce the corresponding tricyclic compound 24a (0.25 g, 64%), mp 166-168 °C. IR (KBr): 3736, 3443 (broad), 2933 (broad), 2358, 1747, 1710, 1647 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.57-7.05 (m, 9H, Ar-H), 5.72 (s, 1H, H₉b), 4.29 (s, 1H, H₃), 4.27 (q, 2H, CO₂CH₂Me), 2.11 (s, 3H, C-Me) and 1.1 (t, 3H, CO₂CH₂Me). 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. Caled for C₂₂H₂₁NO₂: 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-hexahydrochromeno[4,3-b]pyrrole-2-carboxylic acid (24b). According to the general procedure (method B) using salicylaldehyde 1a, DL-alanine 2a and ethyl (2E)-3-(4-Chloro-phenyl)-2-cyanoacrylate 23b to afford 24b (0.26 g, 61%), mp 176-178 °C. IR (KBr): 3600-2800 (broad), 2356, 1745, 1705, 1617 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.56-7.08 (m, 8H, Ar-H), 5.73 (s, 1H, H₉b), 4.34 (s, 1H, H₃), 4.31 (q, 2H, CO₂CH₂Me), 2.14 (s, 3H, C-Me) and 1.15 (t, 3H, CO₂CH₂Me). 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. Caled for C₂₂H₂₀NO₂Cl: 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 (2E)-2-cyano-3-(4-nitrophenyl)acrylate 23c gave 24c (0.31 g, 71%), mp 160-162 °C. IR (KBr): 3500-2300 (broad), 2357, 1748, 1710, 1616 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 8.43-7.11 (m, 8H, Ar-H), 5.78 (s, 1H, H₉b), 4.57 (s, 1H, H₃), 4.31 (q, 2H, CO₂CH₂Me), 2.19 (s, 3H, C-Me) and 1.15 (t, 3H, CO₂CH₂Me). 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. Caled for C₂₂H₂₀N₂O₂S: 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-hexahydrochromeno[4,3-b]pyrrole-2-carboxylic acid (24d). According to the general procedure (method B) using salicylaldehyde 1a, DL-alanine 2a and ethyl (2E)-2-cyano-3-(4-methoxyphenyl)acrylate 23d formed 24d (0.2 g, 47%), mp 166-168 °C. IR (KBr): 3737, 3442-2500 (broad), 2360, 1748, 1710, 1644 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.56-7.10 (m, 8H, Ar-H), 5.72 (s, 1H, H₉₃), 4.31 (s, 1H, H₃), 4.30 (q, 2H, CO₂CH₂Me), 4.00 (s, 3H, O-Me), 2.14 (s, 3H, C-Me) and 1.16 (t, 3H, CO₂CH₂Me). 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 C₂₃H₂₅NO₅: C, 64.93; H, 4.72; 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-hexahydrochromeno[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-3H-indol-3-ylidene)acetate 23e gave an inseparable isomeric mixture of the cycloaducts 24e and 25e in a 4:5:1 ratio (0.23 g, 53% total yield), mp 148-150 °C. 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 ¹H-NMR data for the isomers 24e and 25e was recorded from the reaction mixture. The major spiroadduct 24e. ¹H-NMR (CDCl₃/TFA) δ: 9.34 (s, 1H, NH), 7.95-7.03 (m, 8H, Ar-H), 6.44 (s, 1H, H₉₃), 4.19 (2q, 1H, H₆₅, -OCH₂Me), 4.10 (2q, 1H, H₆₅, -OCH₂Me), 4.02 (s, 3H, MeOH, solvent), 2.51 (s, 3H, C-Me), 0.96 (t, 3H, -OCH₂Me). The minor spiroadduct 25e. ¹H-NMR (CDCl₃/TFA) δ: 9.58 (s, 1H, NH), 7.95-7.03 (m, 8H, Ar-H), 6.35 (s, 1H, H₃), 4.50 (2q, 1H, H₆₅, -OCH₂Me), 4.30 (2q, 1H, H₆₅, -OCH₂Me), 2.13 (s, 3H, C-Me), 1.22 (t, 3H, -OCH₂Me).

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-3H-indol-3-ylidene)acetate 23f afforded 24f (0.24 g, 47%), mp 202-204 °C. IR (KBr): 3737, 3253-2631 (broad), 2361, 1749, 1715, 1689, 1608 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 9.51 (s, 1H, NH), 8.14-7.12 (m, 13H, Ar-H), 6.58 (s, 1H, H₉₃), 4.30 (d, 1H, J = 14.1 Hz, H₅, C-CH₂Ph), 4.25 (2q, 1H, H₆₅, -OCH₂Me), 4.14 (2q, 1H, H₆₅, -OCH₂Me), 3.92 (d, 1H, J = 14.1 Hz, H₆₅, C-CH₂Ph), and 1.01 (t, 3H, -OCH₂Me). Anal. Calcd for C₂₉H₂₅N₂O₅: 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 °C. 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$_2$OH), 3.71 (t, 1H, H$_3$), 3.74 (d, 1H, J = 11.7 Hz, H$_B$, -CH$_2$OH), and 3.46 (d, 1H, J = 7.8 Hz, H$_i$). 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$_2$O$_6$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.80; H, 4.76; N, 7.31.

**4-(2-Hydroxyphenyl)-2-(1H-imidazol-4-ylmethyl)-6,8-dioxo-7-phenyl-3,7-diazabicyclo[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 °C. IR (KBr) 3821, 3618, 3472-3155 (broad), 2356, 1701, and 1616 cm$^{-1}$. 1H-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$_2$), 4.55 (t, 1H, H$_3$), 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$_4$O$_5$: 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%), mp 282-284 °C. IR (KBr) 3737, 3440 (broad), 2357, 1780, 1710, and 1637 cm$^{-1}$. 1H-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$_3$), 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$_{23}$H$_{20}$N$_4$O$_5$: 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-4H-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%), mp 280-282 °C. IR (KBr) 3471 (broad), 2355, 1741, and 1621 cm$^{-1}$. 1H-NMR (CDCl$_3$/TFA) δ: 8.54 (s, 1H, chromonyl, -OCH$_3$), 8.21-7.24 (m, 9H, Ar-H), 5.86 (d, 1H, J = 10.2 Hz, H$_4$), 4.40 (t, 1H, H$_3$), 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$_2$O$_6$: 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-4H-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 °C. IR (KBr) 3736, 3450-3236 (broad), 2356, 1713, and 1621 cm⁻¹. ¹H-NMR (DMSO-d₆) δ: 8.3 (s, 1H, chromonyl, -OCH-), 8.10 – 7.15 (m, 9H, Ar-H), 4.38 (d, 1H, J = 7.8 Hz, H₄), 3.98 (d, 1H, J = 6.9 Hz, H₂), 3.77 (t, 1H, H₅), 3.69 (t, 1H, H₁). 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 C₂₂H₁₆N₂O₆: 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-4H-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 (R¹ = CH₂SH) 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 (R¹ = CH₂SSCH₂CH(NH₂)COOH) as α-amino acid. Colourlss crystals from methanol, mp 256-258 °C. IR (KBr) 3736, 3446 (broad), 1780, 1710, and 1636 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 8.49 (s, 1H, chromonyl, -OCH-), 8.20-7.19 (m, 9H, Ar-H) 5.82 (d, 1H, J = 10.2 Hz, H₄), 4.54-4.34 (m, 3H, H₅ + SCH₂CH- + H₁), 4.4 (d, 1H, J = 15.30 Hz, H₆A, -CH₂S-), 3.9 (d, 1H, J = 15.9 Hz, H₆B, -CH₂S-), 3.7(dd,1H, J = 9.90 and 19.50 Hz, H₆A, -SCH₂-) and 2.9 (dd, 1H, J = 5.40 and 19.20 Hz, H₆B, -SCH₂-). 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 C₂₆H₂₃N₃O₈S₂: 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 °C. 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: ¹H-NMR (CDCl₃/TFA) δ: 7.69-6.93 (m, 4H, Ar-H), 6.12 (s, 1H, H₂), 5.1 (dd, 1H, J = 6.3 and 7.2 Hz, H₄), 3.81 (dd, 1H, J = 8.4 and 8.1 Hz, H₆A, CH₂S), and 3.67 (dd, 1H, J = 5.7 Hz, H₆B, CH₂S). The minor isomer (31): ¹H-NMR (CDCl₃/TFA) δ: 7.69-6.93 (m, 4H, Ar-H), 6.20 (s, 1H, H₂), 5.15 (t, 1H, H₄), 3.89 (d, 1H, J = 7.5 Hz, H₆A, CH₂S), and 3.85 (d, 1H, J = 7.5 Hz, H₆B, CH₂S).

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 MgSO₄. The solvent was evaporated under reduced pressure to afford nearly a quantitative yield (0.38 g, 100%) of the corresponding ester 33. Colourless needles (CH₂Cl₂/pet-ether 40-60), m.p. 190-192 °C. IR (KBr) 3550, 3350, 1780, 1740, and 1710 cm⁻¹. ¹H-NMR (CDCl₃) δ: 7.45-6.84 (m, 9H, Ar-H), 4.99 (d, 1H, J = 9.9 Hz, H₅), 3.83 (s, 3H, CO₂Me), 3.72 (t, 1H, H₃), 3.48 (d, 1H, J = 8.1 Hz, H₁), 1.73 (s, 3H, C-Me), and 1.57 (s broad, 1H, NH). Anal. Calcd for C₂₁H₂₉N₂O₅: 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 (CH₂Cl₂/pet-ether 40-60) as a colourless crystals, m.p. 230-232 °C. IR (KBr) 3650, 1790, 1770, and 1715 cm⁻¹. ¹H-NMR (CDCl₃) δ: 7.54-6.90 (m, 14H, Ar-H), 5.75 (broad, 1H, H₄), 4.54 (t broad, 1H, H₃), 4.10 (s, 3H, MeOH, solvent), 4.08 (d, 1H, H₁), 4.06 (s, 3H, CO₂Me), 2.18 (s, 3H, C-Me). Anal. Calcd for C₂₈H₂₅N₃O₅S: 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(7H)-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 thiodyantoin 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 thiodyantoin derivative 36. Crystallization from (CH₂Cl₂/pet-ether 40-60) to give colourless crystals, m.p. 294-296 °C. IR (KBr) 3600-3500 (broad), 1790, 1750, and 1715 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 8.88-8.12 (m, 5H, pyridine), 7.53-6.81 (m, 14H, Ar-H), 5.84 (d, 1H, H₃), 4.84(t, 1H, H₅a), 4.23 (d, 1H, J = 8.4 Hz, H₈a), 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 C₂₉H₂₃N₃O₈S 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 (Ar¹ = Ph) as a dipolarophile. Colourless crystals from aqueous
methanol, mp 204-206 °C. IR (KBr) 3600-2943 (broad), 2356, and 1617 cm⁻¹. ¹H-NMR (DMSO-d₆) δ: 7.54-6.80 (m, 9H, Ar-H), 5.29 (t, 1H, H₄), 5.04 (d, 1H, J = 8.1 Hz, H₃), 4.32 (d, 1H, J = 7.8 Hz, H₂) 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-d₆, 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 C₁₈H₁₈N₂O₅: C, 63.16; H, 5.30; N, 7.29. 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 (Ar₁ = 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 °C. IR (KBr) 3736, 3443 (broad), 2300, and 1616 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.62-7.10 (m, 14H, Ar-H), 6.28 (t, 1H, H₄), 5.46 (d, 1H, J = 10.2 Hz, H₃), 4.79 (d, 1H, J = 10.2 Hz, H₂) and 3.11 (s, 2H, C-CH₂Ph). 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 C₂₉H₂₂N₂O₅: 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 (Ar₁ = 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 °C. IR (KBr) 3448-3146 (broad), 2350, and 1617 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.52-6.99 (m, 9H, Ar-H), 6.11 (t, 1H, H₄), 5.47 (d, 1H, J = 10.5 Hz, H₃), 4.60 (d, 1H, J = 10.5 Hz, H₂), 1.93 (dd, 1H, J = 4.2 and 15.0 Hz, H₆), 1.76 (m, 1H, -CH₂CH₂Me₂), 1.59 (dd, 1H, J = 8.1 and 15.0 Hz, H₇, C-CH₂CH₂Me₂), 0.93 (d, 3H, J = 6.6 Hz, CHMe₂) and 0.82 (d, 3H, J = 6.3 Hz, CH₃). 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 C₂₃H₂₄N₂O₅: 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 (Ar₁ = 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 °C. IR (KBr) 3438-3136 (broad), 2350, and 1617 cm⁻¹. ¹H-NMR (CDCl₃/TFA) δ: 7.56-7.06 (m, 9H, Ar-H), 6.24 (t, 1H, H₄), 5.55 (d, 1H, J = 10.5 Hz, H₃), 4.71 (d, 1H, J = 10.5 Hz, H₂), 2.62 (t, 2H, CH₂CH₂S), 2.28 (dd, 1H, J = 7.8 and 15.3 Hz, H₆, CH₂CH₂S), 2.08 (dd, 1H, J = 6.6 and 15.6 Hz, H₇, CH₂CH₂S), 2.04 (s, 3H, SMe). MS (m/z %): 402 (M⁺, 7), 357 (M-45, 36), 310
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References


