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# N-Acyliminium Ion Chemistry: Improving the Access to Unsaturated $\gamma$ -Lactams and Their N- $\alpha$ -Methoxylated Derivatives: Application to an Expeditive Synthesis of ( $\pm$ )-Crispine A

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# *N*-Acyliiminium Ions Chemistry: Improving the Access to Unsaturated $\gamma$ -Lactams and their *N*- $\alpha$ -Methoxylated Derivatives. Application to an Expeditive Synthesis of ( $\pm$ )-Crispine A

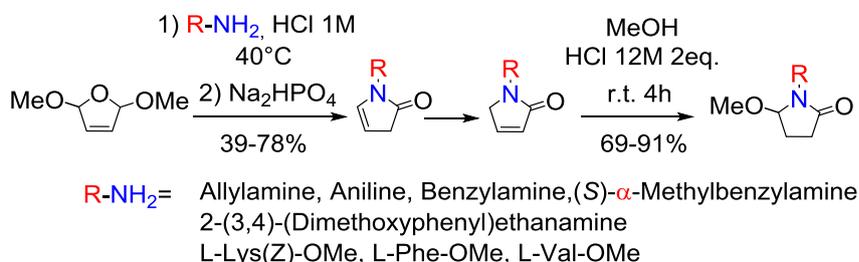
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Dedicated to Dr Jacques Royer

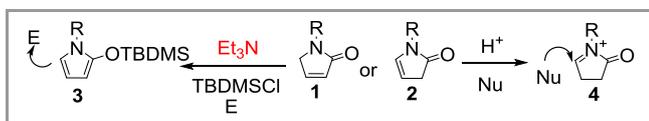


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**Abstract** We describe an improved synthesis of unsaturated  $\gamma$ -lactams by condensation of various primary amines with 2,5-dimethoxy-2,5-dihydrofuran. A modified mechanism for this reaction is suggested. Synthesis of their *N*- $\alpha$ -methoxylated derivatives, as *N*-acyliiminium ions precursors, is also reported. Finally, a short synthesis of ( $\pm$ )-crispine A is presented as an illustrative application.

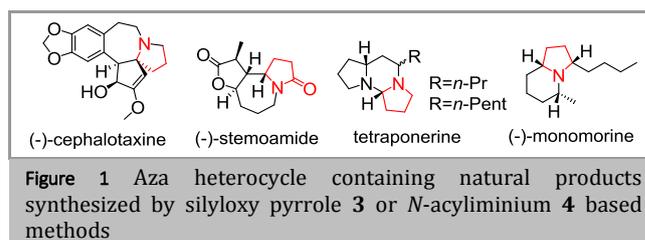
**Key words** unsaturated  $\gamma$ -lactams, aza-heterocycles, *N*-acyliiminium, 5-methoxyppyrolidin-2-one, crispine A

Isomeric unsaturated  $\gamma$ -lactams **1** or **2** are useful building blocks: that can be converted easily into silyloxy pyrroles **3** or *N*-acyliiminium derivatives **4** (Scheme 1).<sup>2</sup>



**Scheme 1** Reactivity of unsaturated  $\gamma$ -lactams **1** or **2**

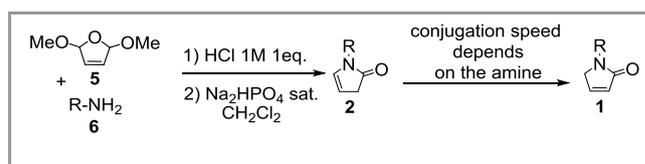
Compound **3** is reactive towards electrophiles (ketone, aldehyde, imine...)<sup>3</sup>; on the other hand, *N*-acyliiminium ion **4** is prone to nucleophilic (allylTMS, silylenolether, diketone, MeOH...) additions.<sup>4</sup> Both reactivities are complementary, giving access to advanced intermediates for the preparation of biologically relevant aza-heterocycles, found in many alkaloid natural products (Figure 1).<sup>5</sup>



**Figure 1** Aza heterocycle containing natural products synthesized by silyloxy pyrrole **3** or *N*-acyliiminium **4** based methods

In 2015, Pelkey and coworkers<sup>6</sup> compiled the known syntheses of 3-pyrrolin-2-ones **1**. Indeed, compounds **1** or **2** can be synthesized by different methods: oxidation of pyrrole ( $R = H, Me$ ),<sup>7</sup> cyclization (especially for synthesis of substituted unsaturated  $\gamma$ -lactams),<sup>8</sup> elimination,<sup>9</sup> via diazo compounds,<sup>10</sup> condensation with 2,5-dimethoxy-2,5-dihydrofuran<sup>11</sup> **5** and metathesis.<sup>12</sup> The last two methods are the most popular for the synthesis of unsubstituted compound **1**.

As discovered twenty years ago in our laboratory,<sup>11a</sup> unsaturated  $\gamma$ -lactams are easily synthesized by condensation between **5** and a primary amine **6** in acidic medium (Scheme 2).



**Scheme 2** Synthesis of unsaturated  $\gamma$ -lactams by condensation with **5**

We searched to improve this reaction and to understand its mechanism. In fact, we wanted to minimize the formation of red polymeric pyrrole side products. For that purpose, we monitored by NMR in  $D_2O$  the reaction between **5** and L-phenylalanine methyl ester hydrochloride **6g** (Table 1, entry 7).

By varying temperature, reaction time and the nature of the base used at the end of the reaction, we found a set of optimized conditions to perform the reaction: 40° C in acid medium (pH = 1) for 7 to 20 minutes (Table 1), following by a neutralization to pH 7 with saturated Na<sub>2</sub>HPO<sub>4</sub> and addition of dichloromethane. Na<sub>2</sub>HPO<sub>4</sub> was chosen instead of NaHCO<sub>3</sub> to decrease the pH from 8 to 7 and to shift the equilibrium from

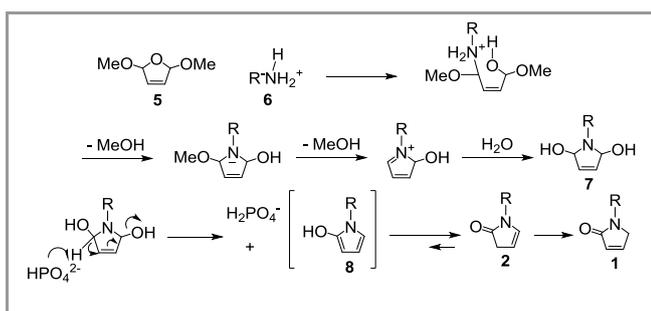
hydroxypyrrole **8** to **2** (Scheme 3). Isolated yields are moderate to good (61% to 78%) except for aniline (entry 2); this finding can be explained by the different pK<sub>a</sub> value of aniline (4.6) and other amines (9-10). Thus all amines with pK<sub>a</sub> of 9-10 should be able to efficiently form unsaturated lactams.

**Table 1** Synthesis of unsaturated  $\gamma$ -lactams

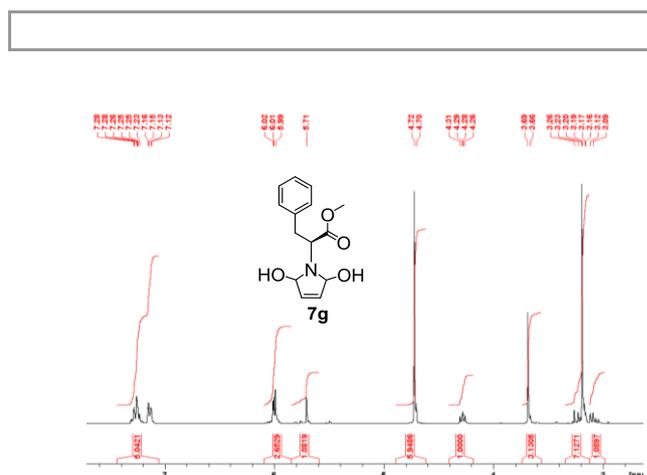
Entry	Amine <b>6</b>	Time (min)	Yield <sup>a</sup> (%)
1	Allylamine <b>6a</b>	15	<b>1a</b> 92 (61)
2	Aniline, HCl <b>6b</b>	7	<b>1b</b> 99 (39)
3	Benzylamine <b>6c</b>	10	<b>1c</b> 95 (67)
4	( <i>S</i> )- $\alpha$ -Methylbenzylamine <b>6d</b>	15	<b>1d</b> 98 (77)
5	2-(3,4)-(Dimethoxyphenyl)ethanamine <b>6e</b>	20	<b>1e</b> 99 (75)
6	L-Lys(Z)-OMe, HCl <b>6f</b>	15	<b>1f</b> 99 (78)
7	L-Phe-OMe, HCl <b>6g</b>	10	<b>1g</b> 95 (67)
8	L-Val-OMe, HCl <b>6h</b>	10	<b>1h</b> 90 (76)

a) Product crude yield (isolated yield)

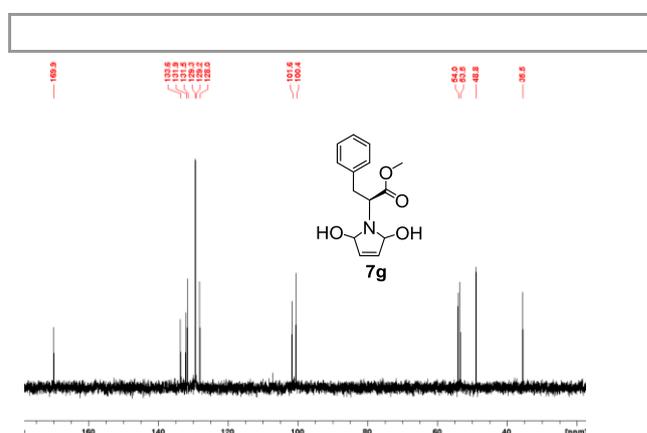
In 1998, Poli *et al.*<sup>11b</sup> hypothesized a mechanism in acetic acid. We suggested some modifications (Scheme 3). In the course of our NMR studies of the reaction, we observed the rapid formation (within a few minutes) of **7** in acidic medium (Figure 2 and 3).<sup>13</sup> The second step consisted of a hydroxyl elimination promoted by hydrogen phosphate dianion acting as a mild base. At first  $\beta,\gamma$ -unsaturated  $\gamma$ -lactam **2** is the only visible product in the spectra. Afterwards, build-up of compound **1** occurred by thermodynamically driven conjugation with the carbonyl group. The kinetics of this isomerization depended on the nature of the amine R residue.



**Scheme 3** Mechanism of the condensation between amine **6** and **5**



**Figure 2** <sup>1</sup>H NMR spectrum of intermediate **7g** in D<sub>2</sub>O



**Figure 3** <sup>13</sup>C NMR spectrum of intermediate **7g** in D<sub>2</sub>O

Pelkey and coworkers reviewed the reactivity of compounds **2** in 2019.<sup>14</sup> Herein, we focused on the possibility to transform

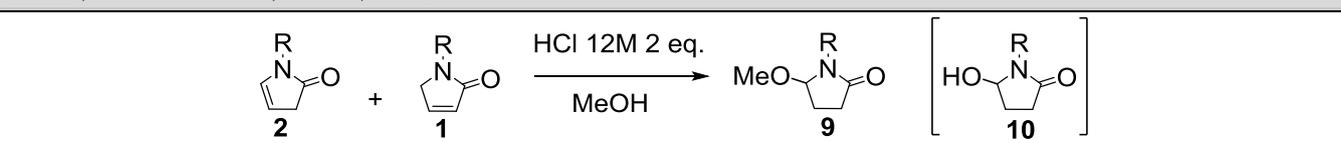
them in *N*-acyliminium ions **4** by treatment with Brønsted acids (Scheme 1). Iminium ion intermediates could be trapped with methanol leading to stable *N*- $\alpha$ -methoxylated derivatives **9** (Table 2).

*N*-acyliminium ions precursors **9** or **10** were mostly synthesized via reduction of succinimides.<sup>15</sup> Typical reducing reagents such as NaBH<sub>4</sub>,<sup>16</sup> DIBAL-H,<sup>17</sup> LiBH<sub>4</sub>,<sup>18</sup> LiEt<sub>3</sub>BH<sup>19</sup> required careful control of temperature and pH to avoid undesired side products. Hydrogenation with Co or Ru catalysis,<sup>20</sup> Zn-catalysis with hydroxysilane<sup>21</sup> were used more

recently. We describe here an alternate practical synthetic route to  $\gamma$ -lactams **9** (table 2).

Treatment of unsaturated  $\gamma$ -lactams **1** or **2** with concentrated (12 M) HCl (2 equivalents) in MeOH for 4 hours at room temperature furnished the *N*- $\alpha$ -methoxylated compounds **9** in good yields (Table 2). The amount of hydrochloric acid has to be kept as small as possible to avoid the formation of *N*- $\alpha$ -hydroxy- $\gamma$ -lactam **10**. This reaction could be performed from crude product **1** or **2**, global yields are almost the same (entry 3 and 7).<sup>22</sup>

**Table 2** Synthesis of *N*- $\alpha$ -methoxylated compounds **9**



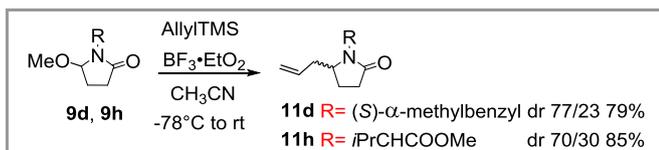
Entry	Lactam <b>1</b>	Product <b>9</b>	Yield <sup>a</sup> (%)	Entry	Lactam <b>1</b>	Product <b>9</b>	Yield <sup>a</sup> (%)
1			69	5			82
2			75	6			81
3			91(65) <sup>b</sup>	7			70 (58) <sup>b</sup>
4			74				

a) Purified product b) From crude **1** or **2**

The procedure is simple, efficient, green and cheap. Indeed, starting materials are inexpensive and neither boron nor any metal catalysis was necessary. Ester and carbamate functions were unaffected unlike in the reduction with hydrides.

*N*- $\alpha$ -methoxylated derivatives **9** could be engaged in nucleophilic addition via *N*-acyliminium ions **4** generated by Brønsted or Lewis acid. To illustrate this application we selected two representative compounds **9d** and **9h** and reacted them with allyltrimethylsilane by using boron trifluoride diethyl

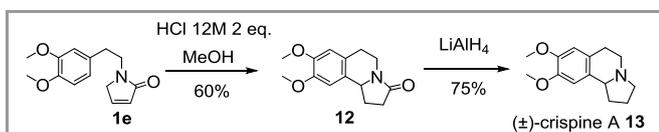
etherate as Lewis acid in acetonitrile (Scheme 4) to give 5-allylpyrrolidin-2-one **11d** and **11h** in good yield (79% and 85% respectively) and moderate diastereoselectivity (dr 77/23 and 70/30). These building blocks could be converted to natural alkaloids<sup>5c,23</sup> or to peptidomimetics<sup>24</sup> by functionalization of the double bond. It should be noted that direct treatment of unsaturated  $\gamma$ -lactams **1** with Lewis acid and allyltrimethylsilane did not provide compounds **11** and only starting material was recovered. Migration of the double bond of unsaturated  $\gamma$ -lactams **1** or **2** requires proton catalysis, thereby addition of Brønsted acid.<sup>5a</sup>



Scheme 4 Addition of allylTMS via *N*-acyliminium ion

Compound **11d** was also obtained from *N*- $\alpha$ -hydroxy- $\gamma$ -lactam **10d** instead of the methoxy derivative **9d**. The reactivities of both these precursors for *N*-acyliminium are very close (90% vs 79% yield, dr 82/18 vs 77/23).<sup>18,23a</sup> However, the synthetic route involving the methoxy derivative **9d** is more convenient, since compound **9d** is easier to handle and to purify, due to its high level of chemical stability compared to the hemiaminal **10d**.

Twenty years ago, Katritzky<sup>25</sup> *et al.* synthesized compound **12** by reaction of **6e**, **5** and benzotriazole followed by cyclization using  $\text{TiCl}_4$  as Lewis acid. Royer<sup>26</sup> *et al.* were able to obtain **12** by refluxing amine **6e** and **5** in acetic acid. In 2016, compound **1e** was obtained by Le Breton *et al.* by metathesis<sup>8b</sup> followed by cyclization using trifluoroacetic acid to give **12**. We took up this synthesis starting from unsaturated  $\gamma$ -lactams **1e** prepared in good yield (75%) as described in Table 1 (entry 5). Treatment of **1e** with two equivalents of concentrated HCl in methanol led to isoquinolinone **12** in 60% yield. The benefits of our synthesis of **12** consist in shorter reaction time, no heating and no use of metal, compared with those described previously. Reduction with  $\text{LiAlH}_4$  gave ( $\pm$ )-crispine A **13** in 75% yield (Scheme 5).<sup>27</sup>



Scheme 5 synthesis of ( $\pm$ )-crispine A

In conclusion, we have developed a practical, scale up (up to 100 mmol on **1f**), low cost, green synthesis of pyrrolidinone  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams **1** and their *N*- $\alpha$ -methoxylated derivatives **9**. These compounds are useful synthetic scaffolds, as exemplified by a 3 steps preparation of racemic crispine A from 2,5-dimethoxy-2,5-dihydrofuran in 34% overall yield.

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All reagents were purchased from commercial suppliers and used without further purification. Acetonitrile was dried on 3Å molecular sieves and stocked under inert atmosphere prior to its use. The reactions were monitored by thin layer chromatography. TLC analyses were performed using aluminium plates coated with silica gel 60F 254 from Macherey Nagel and revealed under ultraviolet light (254 nm) and with a

5% ethanolic phosphomolybdic acid bath. Common silica gel (40-70 mesh) was used for column chromatography purifications. IR spectra were recorded on a Perkin Elmer Spectrum 65 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for  $^1\text{H}$  and at 100 MHz for  $^{13}\text{C}$  and on a Bruker Avance 300 spectrometer operating at 300 MHz for  $^1\text{H}$  and at 75 MHz for  $^{13}\text{C}$ . For  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra analyses,  $\text{CHCl}_3$  (7.26 ppm) and  $^{13}\text{CDCl}_3$  (77.0 ppm) were used as the internal references, respectively. The NMR spectra were processed with TopSpin 3.61 software. High-resolution mass spectra (HRMS) were performed on a Bruker maXi spectrometer by the "Fédération de Recherche" ICOA/CBM (FR2708) platform. Melting points (mp) were measured on a Kofler apparatus. Optical rotation data were obtained on a Perkin Elmer 541 polarimeter at ambient temperature using a 100 mm cell with a 1 mL capacity.

## Procedures

### Experimental procedure for unsaturated $\gamma$ -lactams (**1**) or (**2**)

In a round bottom flask, 5 mmol of amines or amino hydrochloride salts were dissolved in 5 mL of a 1M hydrochloric acid solution (5 mmol) or in 5 mL of water (for hydrochloride salts). A few drops of aqueous HCl 1M could be added to adjust pH to 1. The solution was kept at 40°C and 5 mmol (610  $\mu\text{L}$ ) of 2,5-dimethoxy-2,5-dihydrofuran were added. The reaction was allowed to progress until it became lightly yellow (7 to 20 min.). The solution was then refrigerated with a cool bath (0°C) and the reaction quenched by 5 mL of  $\text{CH}_2\text{Cl}_2$  and 12 mL of a saturated solution of  $\text{Na}_2\text{HPO}_4$ : the pH should increase to 7. The cooling bath was removed and the mixture stirred vigorously for 2 hours at room temperature then extracted with dichloromethane (3 x 30 mL). After drying of the combined organic phases with  $\text{MgSO}_4$ , the solvent was evaporated under vacuum. The crude product could be used without further purification in the next step or purified by flash chromatography on silica gel.

### Experimental procedure for $\alpha$ methoxy- $\gamma$ -lactam synthesis (**9**)

Unsaturated  $\gamma$ -lactams **1** or **2** (6.3 mmol) were dissolved in 25 mL of MeOH. After cooling with an ice bath, 1 mL (12 mmol) of concentrated HCl (12M) was added. The mixture was kept at room temperature under stirring for 4 h. The reaction was quenched with a saturated  $\text{NaHCO}_3$  solution (17 mL, imperatively until pH  $\approx$  8). Most of the MeOH could be evaporated and the mixture extracted with ethyl acetate (2 x 150 mL) then washed with saturated brine. After drying of the combined organic phases with  $\text{MgSO}_4$ , the solvent was evaporated under vacuum. The crude product could be used in the next step or purified by flash chromatography on silica gel.

### Experimental procedure for allylation synthesis, compounds (**11**)

Alpha methoxy- $\gamma$ -lactam (0.5 mmol) was dissolved in 2.5 mL anhydrous acetonitrile cooled at -78°C with a dry ice bath under argon, 158  $\mu\text{L}$  (1 mmol, 2 eq.) of allylTMS was added then 125  $\mu\text{L}$  (1 mmol, 2 eq.) of  $\text{BF}_3 \cdot \text{OEt}_2$ . The mixture was allowed to warm slowly to room temperature under stirring for 3 h. The reaction was quenched with a saturated  $\text{NaHCO}_3$  solution (3 mL) and extracted with ethyl acetate (2x 25 mL). After drying of the combined organic phases with  $\text{Mg}_2\text{SO}_4$ , the solvent was removed under vacuum. Compounds were purified by flash chromatography on silica gel.

The known compounds **1a**, **1b**, **1c**, **1d**, **1e**, **9a**, **9b**, **9c**, **9d**, **11d**, **12**, **13** showed characterization data in full agreement with those previously reported.

### 1-Allyl-1,5-dihydro-2H-pyrrol-2-one (**1a**)<sup>9b</sup>

Following general procedure on 4 mmol of **6a** and after purification by column chromatography on silica gel, a mixture of compounds **1a** and **2a** was obtained as a brown oil in 61% yield (300 mg).

$R_f$  = 0.52 (**2a**), 0.25 (**1a**) (EtOAc).

IR (neat): 2928, 1663, 1415, 1331, 1176, 1060, 989, 928  $\text{cm}^{-1}$ .

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.11 (td, *J* = 5.9, 1.8, 1H, **1a**), 6.40 (td, *J* = 4.9, 2.1, 1H, **2a**), 5.32 (td, *J* = 4.9, 2.5, 1H, **2a**), 5.8 (m, 1H), 5.13-5.26 (m, 2H, **1a**), 4.08 (m, 2H), 3.99 (t, 1.9 Hz, 2H), 3.10 (t, *J* = 2.3 Hz, 2H, **2a**) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 171.3, 133.2 (**1a**), 132.8 (**2a**), 132.7 (**2a**), 128.0 (**1a**), 117.7 (**2a**), 117.6 (**1a**), 143.0 (**1a**), 104.5 (**2a**), 52.5 (**1a**), 44.6 (**1a**), 44.2 (**2a**), 37.5 (**2a**) ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>7</sub>H<sub>10</sub>NO: 124.0757; found: 124.0762.

### 1-Phenyl-1,5-dihydro-2H-pyrrol-2-one (**1b**)<sup>10</sup>

Following general procedure on 5 mmol of **6b** and after purification by column chromatography on silica gel, compound **1b** was obtained as a beige solid in 39% yield (310 mg).

R<sub>f</sub> = 0.46 (CH<sub>2</sub>Cl<sub>2</sub>-EtOAc, 10:1). mp = 90°C.

IR (neat): 3080, 2906, 1683, 1500, 1429, 1371, 1210, 1143, 796, 754, 660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.71 (m, 2H), 7.37 (m, 2H), 7.15 (m, 2H), 6.24 (td, *J* = 6.0, 1.9, 1H), 4.40 (t, *J* = 1.9 Hz, 2H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 170.2, 142.6, 139.1, 129.1, 129.0, 124.2, 118.8, 53.2 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>10</sub>NO: 160.0757; found: 160.0759.

### 1-Benzyl-1,5-dihydro-2H-pyrrol-2-one (**1c**)<sup>9b</sup>

Following general procedure on 20 mmol of **6c** and after purification by column chromatography on silica gel, compound **1c** was obtained as a lightly yellow solid in 67% yield (2.32 g).

R<sub>f</sub> = 0.24 (EtOAc-cyclohexane, 60:40). mp = 60°C.

IR (neat): 3089, 2923, 1699, 1668, 1450, 1404, 1341, 1242, 799, 698 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.42-7.23 (m, 5H), 7.09 (dt, *J* = 6.0, 1.8 Hz, 1H), 6.25 (dt, *J* = 6.0, 1.8 Hz, 1H), 4.67 (s, 2H), 3.92 (t, *J* = 1.7 Hz, 2H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 171.4, 142.9, 137.3, 128.8, 127.9, 127.6, 52.3, 45.9 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>12</sub>NO: 174.0913; found: 174.0919.

### (S)-1-(1-Phenylethyl)-1,5-dihydro-2H-pyrrol-2-one (**1d**)<sup>11b</sup>

Following general procedure on 2.5 mmol of **6d** and after purification by column chromatography on silica gel, compound **1d** was obtained as a yellow oil in 48% yield (225 mg) and compound **2d** in 29% (135 mg).

R<sub>f</sub> = 0.22 (EtOAc-cyclohexane, 50:50).

[α]<sub>D</sub><sup>20</sup> = -154.7 (c = 1.2, CHCl<sub>3</sub>).

IR (neat): 2978, 1685, 1658, 1446, 1239, 1220, 801, 748, 698 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.35-7.19 (m, 5H), 7.01 (dt, *J* = 5.9, 1.8 Hz, 1H), 6.39 (dt, *J* = 5.9, 1.8 Hz, 1H), 5.54 (q, *J* = 7.0 Hz, 1H), 3.91 (dt, *J* = 20.5, 1.8 Hz, 1H), 3.59 (dt, *J* = 20.5, 1.8 Hz, 1H), 1.58 (d, *J* = 7.2 Hz, 3H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 171.1, 143.1, 140.9, 128.6, 127.7, 127.5, 126.9, 48.9, 48.7, 17.8 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>14</sub>NO: 188.1070; found: 188.1073.

### (S)-1-(1-Phenylethyl)-1,3-dihydro-2H-pyrrol-2-one (**2d**)

R<sub>f</sub> = 0.62 (EtOAc-cyclohexane, 50:50).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.39-7.25 (m, 5H), 6.39 (dt, *J* = 5.0, 2.0 Hz, 1H), 5.47 (q, *J* = 7.1 Hz, 1H), 5.28 (dt, *J* = 5.0, 2.4 Hz, 1H), 3.12 (t, *J* = 2.2 Hz, 2H), 1.61 (d, *J* = 7.1 Hz, 3H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 176.5, 140.9, 130.2, 128.7, 127.6, 126.7, 104.6, 49.2, 37.8, 18.8 ppm.

### 1-(3-(3,4-Dimethoxyphenyl)propyl)-1,5-dihydro-2H-pyrrol-2-one (**1e**)<sup>9b</sup>

Following general procedure on 24 mmol of **6e** and after purification by column chromatography on silica gel, compound **1e** was obtained as a yellow oil in 75% yield (4.44 g).

R<sub>f</sub> = 0.21 (EtOAc).

IR (neat): 2934, 1659, 1514, 1451, 1260, 1233, 1139, 1024, 800 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.02 (td, *J* = 6.0, 1.8 Hz, 1H), 6.85-6.72 (m, 3H), 6.18 (td, *J* = 6.0, 1.8 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.80 (tl, *J* = 1.8 Hz, 2H), 3.71 (t, *J* = 7.2 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 171.5, 148.9, 147.6, 142.8, 131.3, 128.1, 120.6, 111.8, 111.3, 55.9, 53.7, 43.9, 34.5 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>18</sub>NO<sub>3</sub>: 248.1287; found: 248.1278.

### Methyl (S)-6-(((benzyloxy)carbonyl)amino)-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoate (**1f**)

Following general procedure on 97 mmol of **6f** and after purification by column chromatography on silica gel, compound **1f** was obtained as a yellow oil in 78% yield (27.3 g).

R<sub>f</sub> = 0.31 (EtOAc-cyclohexane, 70:30).

[α]<sub>D</sub><sup>20</sup> = +3.8 (c = 1, CH<sub>2</sub>Cl<sub>2</sub>).

IR (neat): 3322, 2930, 2864, 1673, 1529, 1444, 1239, 1203, 802, 739, 697 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.36 (m, 5H), 7.15 (dt, *J* = 6.1, 1.7 Hz, 1H), 6.19 (dt, *J* = 6.1, 1.7 Hz, 1H), 5.10 (s, 2H), 4.99 (brt, 1H, NH), 4.90 (dd, *J* = 10.8, 4.9 Hz, 1H), 4.27 (d, *J* = 20.1 Hz, 1H), 3.94 (d, *J* = 20.1 Hz, 1H), 3.73 (s, 3H), 3.19 (dd, *J* = 13.1, 6.7 Hz, 2H), 1.96-2.13 (m, 1H), 1.89-1.74 (m, 1H), 1.58 (m, 2H), δ 1.30 (m, 2H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 172.0, 171.9, 156.5, 144.1, 136.7, 128.5, 128.1, 127.2, 66.6, 53.0, 52.3, 49.7, 40.6, 29.7, 29.2, 23.1 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub>: 361.1758; found: 361.1756.

### Methyl-(S)-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-3-phenylpropanoate (**1g**)

Following general procedure on 10 mmol of **6g** and after purification by column chromatography on silica gel, compound **1g** was obtained as a yellow oil in 65% yield (1.6 g) and compound **2g** in 2% (50 mg).

R<sub>f</sub> = 0.27 (EtOAc-cyclohexane, 50:50).

[α]<sub>D</sub><sup>20</sup> = -36.1 (c = 0.2, CH<sub>2</sub>Cl<sub>2</sub>).

IR (neat): 3029, 2952, 1739, 1682, 1662, 1436, 1241, 1207, 1168, 802, 748, 699 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.36-7.19 (m, 5H), 7.10 (dt, *J* = 6.1, 1.9 Hz, 1H), 6.15 (dt, *J* = 6.1, 1.9 Hz, 1H), 5.24 (dd, *J* = 10.5, 5.8 Hz, 1H), 4.20 (dt, *J* = 19.8, 1.7 Hz, 1H), 3.95 (dt, *J* = 19.8, 1.7 Hz, 1H), 3.76 (s, 3H), 3.45 (dd, *J* = 14.3, 5.8 Hz, 1H), 3.13 (dd, *J* = 14.3, 10.3 Hz, 1H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 171.7, 171.5, 143.9, 136.3, 128.7, 128.6, 127.1, 127.2, 54.4, 52.4, 50.5, 36.1 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>16</sub>NO<sub>3</sub>: 246.1125; found: 240.1124.

### Methyl-(S)-2-(2-oxo-2,3-dihydro-1H-pyrrol-1-yl)-3-phenylpropanoate (**2g**)

R<sub>f</sub> = 0.50 (EtOAc-cyclohexane, 50:50)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.36-7.15 (m, 5H), 6.57 (dt, *J* = 5.1, 2.1 Hz, 1H), 5.29 (dq, *J* = 2.5, 0.5 Hz, 1H), 5.12 (dd, *J* = 9.8, 5.8, 1H), 3.75 (s, 3H), 3.35 (dd, *J* = 14.2, 5.8 Hz, 1H), 3.07 (dd, *J* = 14.2, 5.8 Hz, 1H), 3.00 (t, *J* = 2.3 Hz, 1H), 2.96 (t, *J* = 2.3 Hz, 1H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 176.7, 170.8, 135.9, 130.8, 129.0, 128.6, 127.1, 104.2, 54.5, 52.5, 37.1, 36.9 ppm.

**Methyl-(S)-3-methyl-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)butanoate (1h)**

Following general procedure on 2 mmol of **6h** and after purification by column chromatography on silica gel, compound **2h** was obtained as a yellow oil in 51% yield (200 mg) and compound **1h** in 25% (98 mg).

R<sub>f</sub>: 0.28 (EtOAc-cyclohexane, 50:50).

[α]<sub>D</sub><sup>20</sup> = -61.7 (*c* = 1, CH<sub>2</sub>Cl<sub>2</sub>)

IR (neat): 2963, 2877, 1739, 1669, 1436, 1243, 1199, 1175, 803 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.14 (dt, *J* = 6.0, 1.8 Hz, 1H), 6.15 (dt, *J* = 6.0, 1.8 Hz, 1H), 4.56 (d, *J* = 10.2 Hz, 1H), 4.33 (dt, *J* = 20.6, 1.7, 1H), 3.99 (dt, *J* = 20.6, 1.7, 1H), 3.68 (s, 3H), 2.2 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 171.8, 171.6, 144.1, 126.9, 59.4, 51.9, 50.2, 29.3, 19.3, 19.0 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>16</sub>NO<sub>3</sub>: 198.1125; found: 198.1126.

**Methyl-(S)-3-methyl-2-(2-oxo-2,3-dihydro-1H-pyrrol-1-yl)butanoate (2h)**

R<sub>f</sub> = 0.57 (EtOAc-cyclohexane, 50:50).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 6.76 (dt, *J* = 4.6, 2.1 Hz, 1H), 5.35 (q, *J* = 2.5 Hz, 1H), 4.58 (d, *J* = 9.4 Hz, 1H), 3.77 (s, 3H), 3.13 (m, 2H), 2.25 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 177.0, 171.2, 131.0, 104.0, 59.0, 52.1, 36.9, 30.4, 19.2, 18.8 ppm.

**Methyl-(2S)-2-(2,5-dihydroxy-2,5-dihydro-1H-pyrrol-1-yl)-3-phenylpropanoate (7g)**

In a NMR tube, 43 mg (0.2 mmol) of L-Phenylalanine methyl ester hydrochloride **6g** were dissolved in 0.6 mL of D<sub>2</sub>O. A few drops of HCl 1M were added to adjust pH to 1, followed by 25 μL (0.2 mmol) of 2,5-dimethoxy-2,5-dihydrofuran. After 10 min at 25°C, the reaction was complete (see NMR spectra).

<sup>1</sup>H NMR (D<sub>2</sub>O, 300 MHz): δ = 7.28-7.23 (m, 3H), 7.15-7.12 (m, 2H), 6.00 (m, 3H), 5.70 (m, 1H), 4.70 (s, 2H), 4.28 (dd, *J* = 7.5, 6.0 Hz, 1H), 3.68 (s, 3H), 3.22 (m, 1H), 3.19 (s, 6H, MeOH), 3.11 (m, 1H) ppm.

<sup>13</sup>C NMR (D<sub>2</sub>O, 75 MHz): δ = 169.9, 133.6, 131.9, 131.5, 129.3, 129.2, 128.0, 101.6, 100.4, 54.0, 53.5, 48.8 (MeOH), 35.5 ppm.

**1-Allyl-5-methoxypyrrolidin-2-one (9a)<sup>16b</sup>**

Following general procedure on 1.54 mmol of purified **1a**, after evaporation, compound **9a** was obtained as a lightly yellow oil in 67 % yield (160 mg).

IR (neat): 2935, 1685, 1444, 1414, 1245, 1188, 1075, 884, 656 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 5.87-5.72 (m, 1H), 5.30-5.19 (m, 2H), 4.93 (dd, *J* = 6.2, 1.4 Hz, 1H), 4.30 (dddd, *J* = 15.3, 4.6, 3.3, 1.7 Hz, 1H), 3.63 (dddd, *J* = 15.3, 7.5, 2.0, 1.0 Hz, 1H), 3.30 (s, 3H), 2.56 (ddd, *J* = 17.2, 9.0, 9.0 Hz, 1H), 2.38 (ddd, *J* = 17.2, 9.7, 3.1 Hz, 1H), 2.26-2.11 (m, 1H), 2.10-1.98 (m, 1H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 174.8, 132.4, 117.9, 89.4, 53.0, 42.8, 29.0, 23.9 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>14</sub>NO<sub>2</sub>: 156.1025; found: 156.1018.

**5-Methoxy-1-phenylpyrrolidin-2-one (9b)<sup>20b</sup>**

Following general procedure (except stirring for 22 h) on 0.7 mmol of purified **1b** and after purification by column chromatography on silica gel, compound **9c** was obtained as a lightly yellow oil in 75 % yield (102 mg).

R<sub>f</sub> = 0.4 (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 10:1).

IR (neat): 2935, 2828, 1698, 1497, 1394, 1293, 1193, 1067, 756, 692 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.54 (m, 2H), 7.40 (m, 2H), 7.24 (m, 1H), 5.34 (dd, *J* = 5.8, 0.8 Hz, 1H), 3.30 (s, 3H), 2.77 (ddd, *J* = 17.3, 9.3, 9.3 Hz, 1H), 2.50 (ddd, *J* = 17.3, 9.5, 2.5 Hz, 1H), 2.35-2.20 (m, 1H), 2.20-2.09 (m, 1H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 174.5, 137.9, 129.0, 126.1, 123.2, 92.0, 53.6, 30.0, 24.4 ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>14</sub>NO<sub>2</sub>: 192.1025; found: 192.1017.

**1-Benzyl-5-methoxypyrrolidin-2-one (9c)<sup>20</sup>**

Following general procedure on 0.8 mmol of crude **1c** and after purification by column chromatography on silica gel, compound **9c** was obtained as a lightly yellow oil in 65 % yield (107 mg).

R<sub>f</sub>: 0.65 (EtOAc).

IR (neat): 2933, 2828, 1691, 1442, 1417, 1244, 1171, 1073, 703 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.40-7.24 (m, 5H), 4.96 (d, *J* = 14.7 Hz, 1H), 4.74 (dd, *J* = 6.1, 1.5 Hz, 1H), 4.03 (d, *J* = 14.7 Hz, 1H), 3.23 (s, 3H), 2.59 (ddd, *J* = 17.2, 8.8, 8.8 Hz, 1H), 2.39 (ddd, *J* = 17.2, 9.5, 3.5 Hz, 1H), 2.17-1.93 (m, 2H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 23.7, 29.0, 43.8, 53.0, 89.0, 127.6, 128.4, 128.7, 136.4, 174.9.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>16</sub>NO<sub>2</sub>: 206.1181; found: 206.1187.

**5-Methoxy-1-((S)-1-phenylethyl)pyrrolidin-2-one (9d)<sup>11b</sup>**

Following general procedure on 1.5 mmol of purified **1d** and after purification by column chromatography on silica gel, compound **9d** was obtained as a yellow oil in 74 % yield (243 mg) as 2 diastereoisomers (dr 33/67).

R<sub>f</sub>: 0.53 (dia major), 0.44 (dia minor) (EtOAc-cyclohexane 70:30).

IR (neat): 2935, 2828, 1691, 1462, 1425, 1244, 1182, 1078, 745 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.46-7.17 (m, 5H), 5.35 (q, *J* = 7.2 Hz, 0.7H, dia major), 5.12 (q, *J* = 7.2 Hz, 0.3H, dia minor), 5.03 (dd, *J* = 6.2, 1.1 Hz, 0.3H, dia minor), 4.46 (m, 0.7H, dia major), 3.13 (s, 2H, dia minor), 2.94 (s, 1H, dia minor), 2.6-2.46 (m, 1H), 2.22-2.36 (m, 1H), 2.17-1.94 (m, 0.6H, dia minor), 1.94-1.82 (m, 1.4H, dia major), 1.65 (d, *J* = 7.2 Hz, 1H, dia minor), 1.61 (d, *J* = 7.2 Hz, 2H, dia major) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 175.0 (dia minor), 174.8 (dia major), 141.4 (dia minor), 139.9 (dia major), 128.6 (dia major), 127.7 (dia major + minor), 128.1 (dia minor), 127.4 (dia major), 127.2 (dia minor), 89.1 (dia major), 88.9 (dia minor), 52.6 (dia major), 52.1 (dia minor), 51.3 (dia minor), 50.5 (dia major), 29.5 (dia minor), 29.2 (dia major), 24.2 (dia minor), 24.0 (dia major), 18.1 (dia major), 17.6 (dia minor) ppm.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>18</sub>NO<sub>2</sub>: 220.1337; found: 220.1341.

**Methyl-(2S)-6-(((benzyloxy)carbonyl)amino)-2-(2-methoxy-5-oxopyrrolidin-1-yl)hexanoate (9f)**

Following general procedure on 18.4 mmol of purified **1f** and after purification by column chromatography on silica gel, compound **9f** was obtained as a yellow oil in 82 % yield (5.9 g) as 2 diastereoisomers (dr 53/47).

Rf: 0.4 (EtOAc-cyclohexane, 70:30).

IR (neat): 3339, 2948, 1693, 1243, 1075, 731, 697 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.37 (m, 5H) 5.12 (m, 2H), 4.88 (Brd, 1H, NH), 4.86 (Brd, *J* = 5.4 Hz, 0.8H), 4.69 (dd, *J* = 5.3, 10.0 Hz, 0.6H), 4.49 (dd, *J* = 9.1, 6.1 Hz, 0.5H), 3.78 (s, 1.4H, dia minor), 3.71 (s, 1.6H, dia major), 3.29 (s, 1.4, dia minor), 3.26 (s, 1.6H, dia major), 3.19 (m, 2H), 2.60 (m, 1H), 2.43-2.28 (m, 1H), 2.23-1.78 (m, 4H), 1.66-1.26 (m, 4H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 176.1, 175.1, 171.8, 171.3, 156.5, 136.6, 128.5, 128.1, 90.3, 88.9, 66.6, 54.1, 53.9, 53.5, 52.7, 52.4, 52.3, 40.6, 40.5, 30.0, 29.3, 29.2, 28.8, 28.4, 27.4, 24.5, 24.3, 23.2, 23.0 ppm.

HRMS (ESI): *m/z* [M +Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>28</sub>NNaO<sub>6</sub>: 415.1840; found: 415.1838.

#### Methyl-(2*S*)-2-(2-methoxy-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (**9g**)

Following general procedure on 6.3 mmol of purified **1g** and after purification by column chromatography on silica gel, compound **9g** was obtained as a yellow oil in 81% yield (1.41 g) as 2 diastereoisomers dr 57/43.

Rf: 0.3 (EtOAc-cyclohexane, 40:60).

IR (neat): 2950, 1739, 1694, 1436, 1416, 1240, 1194, 1169, 1075, 749, 699 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.18-7.36 (m, 5H), 4.92 (m, 0.83H, dia minor), 4.50 (dd, *J* = 9.5, 6.5 Hz, 0.58H, dia major), 4.41 (t, *J* = 3.7 Hz, 0.58H, dia major), 3.75 (s, 1.7H, dia major), 3.71 (s, 1.3H, dia minor), 3.27-3.47 (m, 2H), 3.22 (s, 1.7H, dia major), 3.16 (s, 1.3H, dia minor), 2.46-2.62 (m, 1H), 2.17-2.35 (m, 1H), 1.89-2.02 (m, 2H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 23.9 (dia minor), 24.0 (dia major), 28.7 (dia minor), 28.8 (dia major), 34.1 (dia minor), 35.7 (dia major), 52.4 (dia minor), 52.5 (dia major), 52.5 (dia major), 53.7 (dia minor), 56.6 (dia major), 88.7 (dia minor), 90.6 (dia major), 126.7 (dia minor), 126.8 (dia major), 128.5, 128.9, 129.1, 136.8 (dia minor), 137.7 (dia major), 170.7 (dia major), 171.0 (dia minor), 174.9 (dia minor), 175.0 (dia major).

HRMS (ESI): *m/z* [M +Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>19</sub>NNaO<sub>4</sub>: 300.1206; found: 300.1205.

#### Methyl-(2*S*)-2-(2-methoxy-5-oxopyrrolidin-1-yl)-3-methylbutanoate (**9h**)

Following general procedure on 6.4 mmol of purified **1h** and after purification by column chromatography on silica gel, compound **9h** was obtained as a yellow oil in 70% yield (1.08 g) as 2 diastereoisomers (dr 60/40).

Rf: 0.32 (dia major), 0.41 (dia minor), (EtOAc-cyclohexane 50:50).

IR (neat): 2955, 2829, 1740, 1699, 1415, 1243, 1192, 1174, 1072 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): 4.81 (m, 0.6H, dia major), 4.81 (m, 0.34H, dia minor), 4.43 (d, 0.34H, *J* = 10.9 Hz, dia minor), 4.31 (d, 0.6H, *J* = 9.4 Hz, dia major), 3.71 (s, 1.1H, dia minor), 3.68 (s, 1.9H, dia major), 3.31 (s, 1.1H, dia minor), 3.20 (s, 1.9H, dia major), 2.60 (m, 1H), 2.40-2.22 (m, 2H), 2.09-2.00 (m, 2H), 1.01 (d, 1.9H, *J* = 6.6 Hz, dia major), 0.98 (d, 1.1H, *J* = 6.8 Hz, dia minor), 0.96 (d, 1.1H, *J* = 6.8 Hz, dia minor), 0.81 (d, 1.9H, *J* = 6.6 Hz, dia major) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 175.9 (dia minor), 175.0 (dia major), 171.5 (dia minor), 170.8 (dia major), 90.3 (dia minor), 88.5 (dia major), 58.3 (dia major), 54.2 (dia major), 54.0 (dia minor), 52.0 (dia major), 51.8 (dia minor), 29.8 (dia minor), 28.3 (dia major and minor), 27.0 (dia major), 24.7 (dia minor), 24.6 (dia major), 19.8 (dia major), 19.7 (dia minor), 19.4 (dia minor), 18.6 (dia major) ppm.

HRMS (ESI): *m/z* [M +Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>19</sub>NNaO<sub>4</sub>: 252.1206; found: 252.1207.

#### 5-Allyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one (**11d**)<sup>19,23a</sup>

Following general procedure on 0.5 mmol and after purification by column chromatography on silica gel, compound **11d** was obtained as a colorless oil in 79% yield (90 mg) as 2 diastereoisomers dr 77/23.

Rf: 0.38 (EtOAc-cyclohexane, 50:50).

IR (neat): 2974, 2935, 1675, 1411, 1260, 1026, 699 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): 7.45-7.23 (m, 5H), 5.70-5.38 (m, 2H), 5.11-4.85 (m, 2H), 3.79 (tt, *J* = 8.2, 3.2 Hz, 0.77H, dia major), 3.34 (tt, *J* = 8.2, 3.1 Hz, 0.23H, dia minor), 2.59-2.44 (m, 1H), 2.41-2.27 (m, 1H), 2.17-2.01 (m, 1H), 1.98-1.85 (m, 1H), 1.83-1.67 (m, 2H), 1.66 (d, *J* = 7.1 Hz, 3H) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 175.4 (dia major), 175.3 (dia minor), 141.9 (dia major), 139.7 (dia minor), 133.3 (dia major), 133.2 (dia minor), 128.6 (dia minor), 128.4 (dia major), 127.6 (dia minor), 127.4 (dia major), 127.2 (dia major), 118.2 (dia major), 56.5 (dia minor), 56.2 (dia major), 50.6 (dia minor), 49.4 (dia major), 39.6 (dia minor), 38.8 (dia major), 30.3, 23.9 (dia major), 23.7 (dia minor), 18.3 (dia minor), 16.3 (dia major) ppm.

HRMS (ESI): *m/z* [M +H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>20</sub>NO: 230.1545; found: 230.1548.

#### Methyl-(2*S*)-2-(2-allyl-5-oxopyrrolidin-1-yl)-3-methylbutanoate (**11h**)

Following general procedure on 0.5 mmol and after purification by column chromatography on silica gel, compound **11h** was obtained as a colorless oil in 85% yield (102 mg) as 2 diastereoisomers (dr 70/30).

Rf: 0.5 (EtOAc-cyclohexane, 50:50).

IR (neat): 2965, 2875, 1739, 1686, 1412, 1252, 1203, 1008, 916 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 5.84-5.62 (m, 1H), 5.21-5.10 (m, 2H), 4.36 (d, *J* = 10.7 Hz, 0.3H, dia minor), 4.10 (d, *J* = 10.2 Hz, 0.7H, dia major), 3.74 (s, 2.1H, dia major), 3.72 (s, 1.0H, dia minor), 3.77-3.71 (m, 0.3H, dia minor), 3.70-3.60 (m, 0.7H, dia major), 2.70-2.60 (m, 0.7H, dia major), 2.54-2.03 (m, 5.6H), 1.92-1.76 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 0.9H, dia minor), 1.04 (d, *J* = 6.6 Hz, 2.1H, dia major), 0.96 (d, *J* = 6.6 Hz, 2.1H, dia major), 0.88 (d, *J* = 6.6 Hz, 0.9H, dia minor) ppm.

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 176.0 (dia minor), 175.6 (dia major), 171.7 (dia minor), 170.5 (dia major), 133.4 (dia major), 133.3 (dia minor), 118.6 (dia minor), 118.5 (dia major), 61.6 (dia major), 59.8 (dia minor), 59.1 (dia major), 56.3 (dia minor), 51.9, 38.5 (dia major), 37.8 (dia minor), 29.6 (dia major), 29.5 (dia minor), 29.1 (dia major), 26.7 (dia minor), 24.2 (dia minor), 24.0 (dia major), 20.5 (dia major), 20.1 (dia minor), 19.3 (dia minor), 19.2 (dia major) ppm.

HRMS (ESI): *m/z* [M +H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>22</sub>NO<sub>3</sub>: 240.1594; found: 240.1596.

#### 8,9-Dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**12**)<sup>8b, 25,26</sup>

Following general procedure on 0.5 mmol on purified **1e** and after purification by column chromatography on silica gel, compound **12** was obtained as a brown solid in 60% yield (72 mg).

Rf: = 0.22 (EtOAc). mp = 100-104°C.

IR (neat): 2937, 1674, 1513, 1417, 1253, 1229, 1117, 1027, 1005, 861, 766 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 6.60 (s, 1H), 4.76 (t, *J* = 7.5 Hz, 1H), 4.33 (dd, *J* = 12.2, 5.1 Hz, 1H), 3.90 (s, 3H), 6.65 (s, 1H), 3.89 (s, 3H), 3.04 (ddd, *J* = 11.9, 11.9, 4.4 Hz, 1H), 2.90 (ddd, *J* = 11.4, 11.4, 5.5 Hz, 1H), 2.77-2.43 (m, 4H), 1.86 (m, 1H) ppm.

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  = 173.2, 148.1, 147.9, 129.3, 125.5, 111.7, 107.6, 56.6, 56.1, 55.9, 37.1, 31.8, 28.1, 27.8 ppm.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{18}\text{NO}_3$ : 248.1281; found: 248.1283.

### ± Crispine A (13)<sup>27</sup>

Under an argon atmosphere, lithium aluminum hydride (50 mg, 1.3 mmol) was dissolved in anhydrous tetrahydrofuran (7 mL) and the solution cooled to 0 °C. Compound 12 (60 mg, 0.24 mmol) dissolved in anhydrous tetrahydrofuran (3 mL) was added dropwise to the hydride solution at 0 °C then the resulting solution heated under reflux for 3 h and stirred for a further 18 h at room temperature. Diethyl ether (3 mL) was added and the reaction was quenched by careful addition of saturated sodium potassium tartrate (0.5 mL). The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtration on a Büchner funnel. The filtrate was evaporated under reduced pressure and the resultant yellow solid was purified by column chromatography on silica gel and 10:1.5  $\text{CH}_2\text{Cl}_2$ /methanol was used as eluent. Compound 13 was obtained as a white solid in 75% yield (42 mg).

Rf: = 0.5 ( $\text{CH}_2\text{Cl}_2$ -MeOH, 10:1.5). mp 86 °C (lit. mp 88–89 °C).

IR (neat): 2936, 2789, 1607, 1508, 1372, 1211, 1135, 1014, 856, 761  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 6.65 (s, 1H), 6.61 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.44 (t,  $J$  = 8.2 Hz, 1H), 3.26–3.17 (m, 1H), 3.17–2.99 (m, 2H), 2.82–2.52 (m, 3H), 2.42–2.29 (m, 1H), 2.07–1.84 (m, 2H), 1.84–1.68 (m, 1H) ppm.

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  = 147.3, 147.2, 131.0, 126.2, 111.3, 108.8, 63.0, 56.0, 55.9, 53.2, 48.4, 30.5, 28.1, 22.2 ppm.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{20}\text{NO}_2$ : 234.1488; found: 234.1493.

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### Supporting Information

YES (this text will be updated with links prior to publication)

### Primary Data

NO (this text will be deleted prior to publication)

### References

- (1) a) Université Paris-Saclay, CNRS, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Laboratoire de Catalyse Moléculaire, Bâtiment 420, 91405 Orsay, France. b) NOVECAL, 86 rue de Paris, 91400 Orsay, France.
- (2) Baussanne, I.; Dudot, B.; Pérard-Viret, J.; Planas, L.; Royer, J. *Arkivoc* **2006**, 57–66.
- (3) Toffano, M.; Dudot, B.; Zaparucha, A.; Royer, J.; Sevrin, M.; George, P.; Chiaroni, A. *Tetrahedron: Asymmetry* **2003**, *14*, 3365–3370.
- (4) (a) Wu, P.; Nielsen, T. E. *Chem. Rev.* **2017**, *117*, 7811–7856. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.
- (5) (a) Planas, L.; Pérard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087–3092. (b) Yoritate, M.; Takahashi, Y.; Tajima, H.; Ogihara, C.; Yokoyama, T.; Soda, Y.; Oishi, T.; Sato, T.; Chida, N. *J. Am. Chem. Soc.* **2017**, *139*, 18386–18391. (c) Bosque, I.; Gonzalez-Gomez, J. C.; Loza, M. I.; Brea, J. *J. Org. Chem.* **2014**, *79*, 3982–3991. (d) Toyooka, N.; Zhou, D.; Nemoto, H. *J. Org. Chem.* **2008**, *73*, 4575–4577.
- (6) Pelkey, E. T.; Pelkey, Sarah, J.; Greger, J. G. *Adv. Heterocycl. Chem.* **2015**, *115*, 151–285.
- (7) Bocchi, V.; Chierici, L.; Gardini, G. P.; Mondelli, R. *Tetrahedron* **1970**, *26*, 4073–4082.
- (8) (a) Rio, G.; Masure, D. *Bull. Soc. Chim. Fr.* **1972**, 4598–4604. (b) Jebali, K.; Planchat, A.; Amri, H.; Mathé-Allainmat, M.; Lebreton, J. *Synthesis* **2016**, *48*, 1502–1517. (c) del Corte, X.; Marigorta, E. M. De; Palacios, F.; Vicario, J.; Corte, X.; Marigorta, E. M. De; Palacios, F.; Vicario, J. *Molecules* **2019**, *24*, 2951.
- (9) (a) Santaniello, E.; Casati, R.; Manzocchi, A. *J. Chem. Soc. Perkin Trans 1* **1985**, 2389–2392. (b) Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011–2022.
- (10) Zhukovsky, D.; Dar'ın, D.; Kantin, G.; Krasavin, M. *European J. Org. Chem.* **2019**, *2019*, 2397–2400.
- (11) (a) Baussanne, I.; Chiaroni, A.; Husson, H. P.; Riche, C.; Royer, J. *Tetrahedron Lett.* **1994**, *35*, 3931–3934. (b) Poli, G.; Baffoni, S. C.; Giambastiani, G.; Reginato, G. *Tetrahedron* **1998**, *54*, 10403–10418. (c) Katritzky, A. R.; Mehta, S.; He, H. Y.; Cui, X. *J. Org. Chem.* **2000**, *65*, 4364–4369. (d) Saygili, N.; Altunbas, A.; Yesilada, A. *Turkish J. Chem.* **2006**, *30*, 125–130. (e) Halie, D.; Pérard-Viret, J.; Royer, J. *Heterocycles* **2006**, 57–66. (f) Alves, J. C. F. *J. Braz. Chem. Soc.* **2007**, *18*, 855–859.
- (12) (a) Petersen, M. T.; Nielsen, T. E. *Org. Lett.* **2013**, *15*, 1986–1989. (b) Gratais, A.; Pannecoucke, X.; Bouzbouz, S. *Synlett* **2014**, *25*, 1555–1560. (c) Ye, L. W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem.* **2014**, *12*, 1833–1845.
- (13) Integration area at 5.7 and 6.0 ppm accounts for 3.6 protons instead of 4, as reaction took place in  $\text{D}_2\text{O}$  and some deuterium was incorporated. A HSQC spectrum (see supporting information) confirmed the structure.
- (14) Pelkey, E. T.; Pelkey, S. J.; Greger, J. G. *Adv. Heterocycl. Chem.* **2019**, *128*, 433–565.
- (15) Zaragoza-Galicia, I.; Santos-Sánchez, Z. A.; Hidalgo-Mercado, Y. I.; Olivo, H. F.; Romero-Ortega, M. *Synthesis* **2019**, *51*, 4650–4656.
- (16) (a) Hubert, J. C.; Steege, W.; Speckamp, W. N.; Huisman, H. O. *Synth. Commun.* **1971**, *1*, 103–109. (b) Berthet, M.; Beauseigneur, A.; Moine, C.; Taillier, C.; Othman, M.; Dalla, V. *Chem. - A Eur. J.* **2018**, *24*, 1278–1282.
- (17) Bennett, D. J.; Blake, A. J.; Cooke, P. A.; Godfrey, C. R. A.; Pickering, P. L.; Simpkins, N. S.; Walker, M. D.; Wilson, C. *Tetrahedron* **2004**, *60*, 4491–4511.
- (18) Bailey, P. D.; Baker, S. R.; Boa, A. N.; Clayson, J.; Rosair, G. M. *Tetrahedron Lett.* **1998**, *39*, 7755–7758.
- (19) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. J. *J. Org. Chem.* **1990**, *55*, 215–223.
- (20) (a) Holsten, M.; Beller, M.; Papa, V.; Junge, K.; Adam, R.; Cabrero-Antonino, J. R. *Chem. Sci.* **2017**, *8*, 5536–5546. (b) Cabrero-Antonino, J. R.; Sorribes, I.; Junge, K.; Beller, M. *Angew. Chemie - Int. Ed.* **2016**, *55*, 387–391.
- (21) Ding, G.; Lu, B.; Li, Y.; Wan, J.; Zhang, Z.; Xie, X. *Adv. Synth. Catal.* **2015**, *357*, 1013–1021.
- (22) The reaction with aqueous HCl 12M could be done in ethanol to give *N*- $\alpha$ -ethoxylated derivatives and in acetonitrile to obtain the *N*- $\alpha$ -hydroxylated derivatives with less efficiency.
- (23) (a) Butters, M.; Davies, C. D.; Elliott, M. C.; Hill-Cousins, J.; Kariuki, B. M.; Ooi, L. L.; Wood, J. L.; Wordingham, S. V. *Org. Biomol. Chem.* **2009**, *7*, 5001–5009. (b) Kotha, S.; Pulletikurti, S. *Synthesis* **2019**, *51*, 3981–3988.
- (24) Toum, V.; Bolley, J.; Lalatonne, Y.; Barbey, C.; Motte, L.; Lecouvey, M.; Royer, J.; Dupont, N.; Pérard-Viret, J. *Eur. J. Med. Chem.* **2015**, *93*, 360–372.
- (25) Katritzky, A. R.; Mehta, S.; He, H. Y. *J. Org. Chem.* **2001**, *66*, 148–15.
- (26) Fontaine, H.; Baussanne, I.; Royer, J. *Synth. Commun.* **1997**, *27*, 2817–2824.

- (27) (a) Allin, S. M.; Gaskell, S. N.; Towler, J. M. R.; Bulman Page, P. C.; Saha, B.; McKenzie, M. J.; Martin, W. P. *J. Org. Chem.* **2007**, *72*, 8972–8975. (b) Mons, E.; Wanner, M. J.; Ingemann, S.; Maarseveen, J. H. Van; Hiemstra, H. *J. Org. Chem.* **2014**, *79*, 7380–7390.