Synthesis F. Souquet et al. PSP

N-Acyliminium Ion Chemistry: Improving the Access to Unsaturated γ-Lactams and Their *N*-α-Methoxylated Derivatives: Application to an Expeditive Synthesis of (±)-Crispine A

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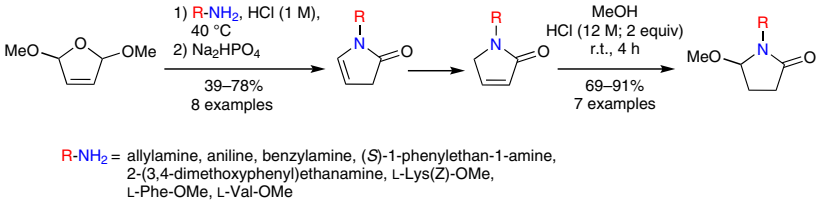
Dedicated to Dr. Jacques Royer

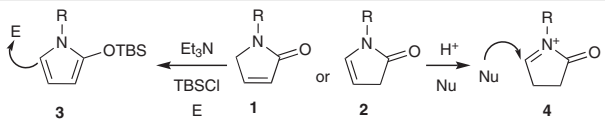


Received: 01.04.2020
Accepted after revision: 20.05.2020
Published online: 23.06.2020
DOI: 10.1055/s-0040-1707886; Art ID: ss-2020-t0173-psp

Abstract An improved synthesis of unsaturated γ-lactams by condensation of various primary amines with 2,5-dimethoxy-2,5-dihydrofuran is described. A modified mechanism for this reaction is suggested. Synthesis of their *N*-α-methoxylated derivatives, as *N*-acyliminium ion precursors, is also reported. Finally, a short synthesis of (±)-crispine A is presented as an illustrative application.

Key words unsaturated γ-lactams, aza-heterocycles, *N*-acyliminium, 5-methoxypyrrolidin-2-one, crispine A

Isomeric unsaturated γ-lactams **1** or **2** are useful building blocks that can be converted easily into silyloxy pyrroles **3** or *N*-acyliminium derivatives **4** (Scheme 1).[2]



Scheme 1 Reactivity of unsaturated γ-lactams **1** or **2**

Compound **3** is reactive towards electrophiles (ketone, aldehyde, imine, etc.);[3] on the other hand, *N*-acyliminium ion **4** is prone to nucleophilic (allylTMS, silyl enol ether, diketone, MeOH, etc.) additions.[4] 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).[5]

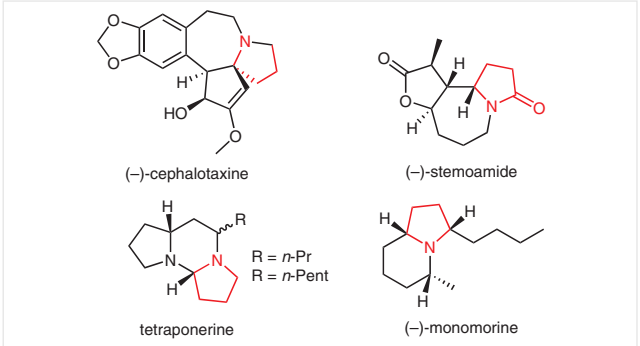


Figure 1 Aza-heterocycle-containing natural products synthesized by silyloxy pyrrole (**3**)- or *N*-acyliminium (**4**)-based methods

In 2015, Pelkey and co-workers[6] 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),[7] cyclization (especially for the synthesis of substituted unsaturated γ-lactams),[8] elimination,[9] via diazo compounds,[10] condensation with 2,5-dimethoxy-2,5-dihydrofuran (**5**),[11] and metathesis.[12] The latter two methods are the most popular for the synthesis of unsubstituted compound **1**.

As discovered twenty years ago in our laboratory,[11a] unsaturated γ-lactams are easily synthesized by condensation between **5** and a primary amine **6** in acidic medium (Scheme 2).

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, the reaction between **5** and L-phenylalanine methyl

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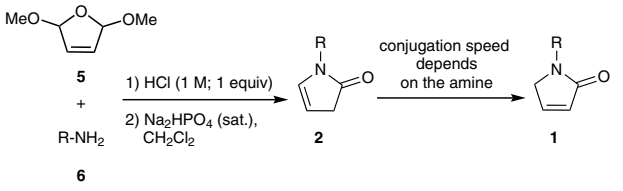


Scheme 2 Synthesis of unsaturated γ-lactams by condensation with **5**

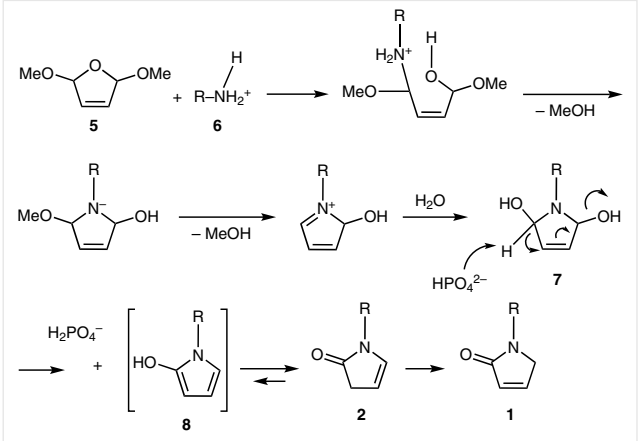
ester hydrochloride (**6g**) was monitored by NMR spectroscopy in D_2O (Table 1, entry 7). By varying the temperature, reaction time, and the nature of the base used at the end of the reaction, a set of optimized conditions was established to perform the reaction: 40 °C in acid medium (pH 1) for 7 to 20 minutes (Table 1), followed by neutralization to pH 7 with saturated aqueous Na_2HPO_4 and addition of dichloromethane. Na_2HPO_4 was chosen instead of $NaHCO_3$ to decrease the pH from 8 to 7 and to shift the equilibrium from hydroxypyrrole **8** to **2** (Scheme 3). Isolated yields were moderate to good (61% to 78%) except for aniline (entry 2); this finding can be explained by the different pK_a value of aniline (4.6) and other amines (9–10). Thus all amines with pK_a of 9–10 should be able to efficiently form unsaturated lactams.

Table 1 Synthesis of Unsaturated γ-Lactams

Entry	Amine **6**	Time (min)	Yield (%)[a]
1	allylamine (**6a**)	15	**1a** 92 (61)
2	aniline·HCl (**6b**)	7	**1b** 99 (39)
3	benzylamine (**6c**)	10	**1c** 95 (67)
4	(*S*)-1-phenylethan-1-amine (**6d**)	15	**1d** 98 (77)
5	2-(3,4-dimethoxyphenyl)ethanamine (**6e**)	20	**1e** 99 (75)
6	L-Lys(Z)-OMe·HCl (**6f**)	15	**1f** 99 (78)
7	L-Phe-OMe·HCl (**6g**)	10	**1g** 95 (67)
8	L-Val-OMe·HCl (**6h**)	10	**1h** 90 (76)

[a] Yield of the crude product. Isolated yield of the pure product (either α,β- or α,β- plus the β,γ-isomer) is given in the parentheses.

In 1998, Poli et al.[11b] 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 (Figures 2 and 3).[13] The second step consisted of a hydroxyl elimination promoted by hydrogen phosphate dianion acting as a mild base. At first β,γ-unsaturated γ-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



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

this isomerization depended on the nature of the amine R residue.

Pelkey and co-workers reviewed the reactivity of compounds **2** in 2019.[14] Herein, we focused on the possibility to

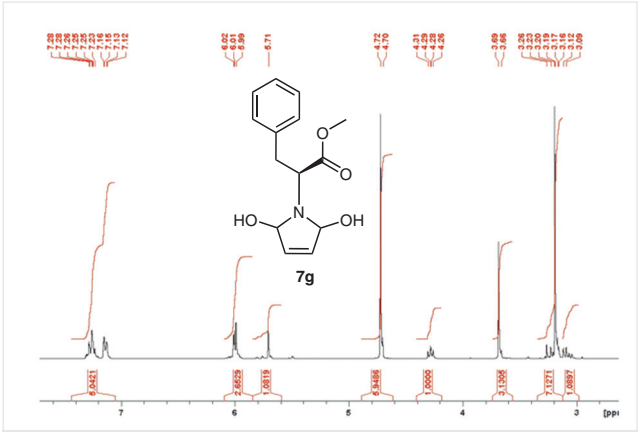


Figure 2 ^1H NMR spectrum of intermediate **7g** in D_2O

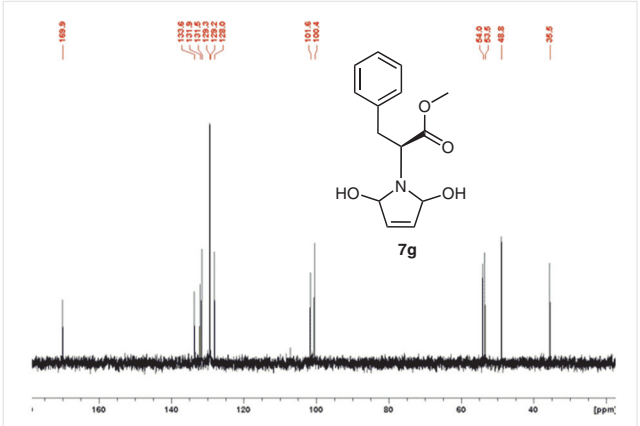


Figure 3 ^{13}C NMR spectrum of intermediate **7g** in D_2O

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

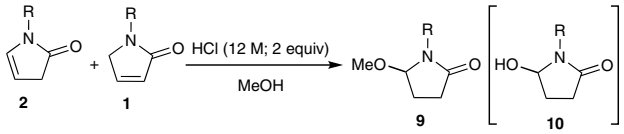
N-Acyliminium ions precursors **9** or **10** were mostly synthesized via reduction of succinimides.[15] Typical reducing reagents such as $NaBH_4$,[16] DIBAL-H,[17] $LiBH_4$,[18] $LiEt_3BH$[19] required careful control of temperature and pH to avoid undesired side products. Hydrogenation with Co or Ru catalysis[20] and Zn catalysis with hydroxysilane[21] were used more recently. We describe here an alternate practical synthetic route to γ-lactams **9** (Table 2).

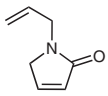
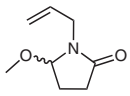
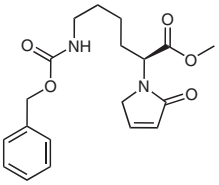
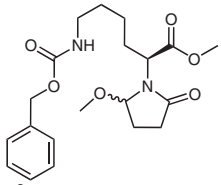
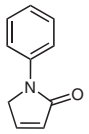
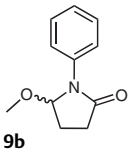
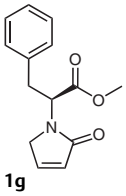
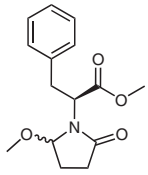
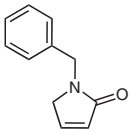
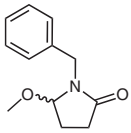
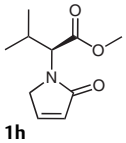
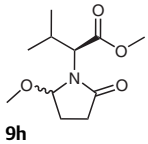
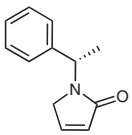
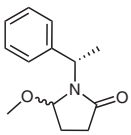
Treatment of unsaturated γ-lactams **1** or **2** with concentrated (12 M) HCl (2 equiv) in MeOH for 4 hours at room temperature furnished the *N*-α-methoxylated compounds **9** in good yields (Table 2). The amount of hydrochloric acid has to be kept as small as possible to avoid the formation of *N*-α-hydroxy-γ-lactam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

The procedure is simple, efficient, green, and cheap – the 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-α-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 allowed them to react with allyltrimethylsilane in the presence of boron trifluoride diethyl etherate as Lewis acid in acetonitrile (Scheme 4) to give 5-allylpyrrolidin-2-ones **11d** and **11h** in good yields (79% and 85%, respectively) and moderate diastereoselectivities (dr 77:23 and 70:30). These building blocks could be converted into natural

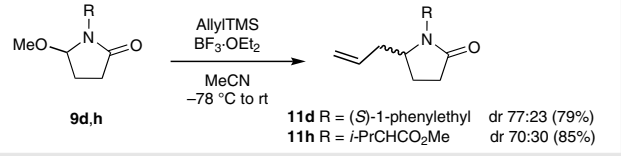
Table 2 Synthesis of *N*-α-Methoxylated Compounds **9**



Entry	Lactam **1**	Product **9**	Yield[a] (%)	Entry	Lactam **1**	Product **9**	Yield[a] (%)
1	 **1a**	 **9a**	67	5	 **1f**	 **9f**	82
2	 **1b**	 **9b**	75	6	 **1g**	 **9g**	81
3	 **1c**	 **9c**	91 (65)[b]	7	 **1h**	 **9h**	70 (58)[b]
4	 **1d**	 **9d**	74				

[a] Purified product.
[b] From crude **1** or **2**.

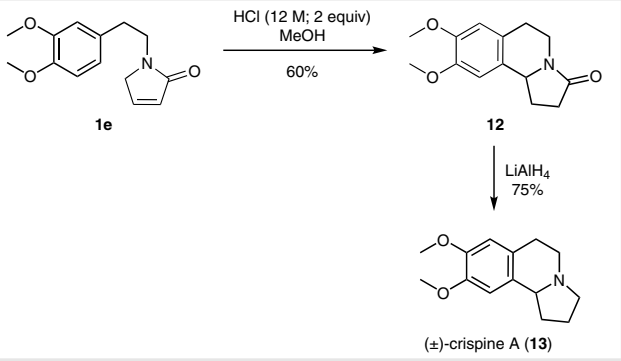
alkaloids[5c,23] or to peptidomimetics[24] by functionalization of the double bond. It should be noted that direct treatment of unsaturated γ-lactams **1** with Lewis acid and allyltrimethylsilane did not provide compounds **11** and only starting material was recovered. Migration of the double bond of unsaturated γ-lactams **1** or **2** requires proton catalysis, therefore addition of Brønsted acid.[5a]



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

Compound **11d** was also obtained from *N*-α-hydroxy-γ-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).[18,23a] 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 et al.[25] synthesized compound **12** by reaction of **6e**, **5**, and benzotriazole followed by cyclization using $TiCl_4$ as Lewis acid. Royer et al.[26] 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[8b] followed by cyclization using trifluoroacetic acid to give **12**. We took up this synthesis starting from unsaturated γ-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 directly to isoquinolinone **12** in 60% yield. The benefits of our synthesis of **12** include shorter reaction time, no heating, and no use of metal, compared with those described previously. Reduction with $LiAlH_4$ gave (±)-crispine A (**13**) in 75% yield (Scheme 5).[27]



Scheme 5 synthesis of (±)-crispine A

In conclusion, we have developed a practical, scalable (up to 100 mmol for **1f**), low cost, green synthesis of pyrolidinone α,β-unsaturated γ-lactams **1** and their *N*-α-methoxylated derivatives **9**. These compounds are useful synthetic scaffolds, as exemplified by a three-step preparation of racemic crispine A from 2,5-dimethoxy-2,5-dihydrofuran in 34% overall yield.

All reagents were purchased from commercial suppliers and used without further purification. MeCN was dried on 3Å molecular sieves and kept under inert atmosphere prior to its use. The reactions were monitored by TLC. TLC analyses were performed using aluminum 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 PerkinElmer Spectrum 65 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C and on a Bruker Avance 300 spectrometer operating at 300 MHz for ^1H and at 75 MHz for ^{13}C. For ^1H and ^{13}C NMR spectra analyses, $CHCl_3$ (7.26 ppm) and $^{13}CDCl_3$ (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 were measured on a Kofler apparatus. Optical rotation data were obtained on a PerkinElmer 541 polarimeter at ambient temperature using a 100 mm cell with a 1 mL capacity.

Unsaturated γ-Lactams 1 or 2; General Procedure

In a round-bottomed flask, amine or amino hydrochloride salt (5 mmol) were dissolved in aq 1 M HCl (5 mL, 5 mmol) or in H_2O (5 mL) (for hydrochloride salts). A few drops of aq 1 M HCl could be added to adjust the pH to 1. The solution was kept at 40 °C and 2,5-dimethoxy-2,5-dihydrofuran (**5**; 5 mmol, 610 μL) was 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 CH_2Cl_2 (5 mL) and sat. aq Na_2HPO_4 (12 mL); the pH should increase to 7. The cooling bath was removed and the mixture stirred vigorously for 2 h at rt and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and 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.

α-Methoxy-γ-lactams 9; General Procedure

Unsaturated γ-lactam **1** or **2** (6.3 mmol) was dissolved in MeOH (25 mL). After cooling with an ice bath, concd HCl (12 M, 1 mL, 12 mmol) was added. The mixture was kept at rt under stirring for 4 h. The reaction was quenched with sat. aq $NaHCO_3$ (17 mL, imperatively until pH ≈ 8). Most of the MeOH was evaporated and the mixture extracted with EtOAc (2 × 150 mL). The combined extracts were washed with brine. After drying the combined organic phases ($MgSO_4$), the solvent was evaporated under vacuum. The crude product could be used in the next step or purified by flash chromatography on silica gel.

Allylation of 9d,h; General Procedure

α-Methoxy-γ-lactam (0.5 mmol) was dissolved in anhyd MeCN (2.5 mL) and cooled to –78 °C with a dry ice bath under argon. AllylTMS (158 µL, 1 mmol, 2 equiv) was added, followed by $BF_3{\cdot}OEt_2$ (125 µL, 1 mmol, 2 equiv). The mixture was allowed to warm slowly to rt under stirring for 3 h. The reaction was quenched with sat. aq $NaHCO_3$ (3 mL) and extracted with EtOAc (2 × 25 mL). After drying the combined organic phases ($MgSO_4$), 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-2*H*-pyrrol-2-one (1a)[9b]

Following the general procedure on **6a** (228 mg, 4 mmol) and after purification by column chromatography on silica gel, a mixture of compounds **1a** and **2a** was obtained as a brown oil; yield: 300 mg (61%); R_f = 0.52 (**2a**), 0.25 (**1a**) (EtOAc).

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

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.11 (td, *J* = 5.9, 1.8 Hz, 1 H, **1a**), 6.40 (td, *J* = 4.9, 2.1 Hz, 1 H, **2a**), 5.32 (td, *J* = 4.9, 2.5 Hz, 1 H, **2a**), 5.8 (m, 1 H), 5.13–5.26 (m, 2 H, **1a**), 4.08 (m, 2 H), 3.99 (t, *J* = 1.9 Hz, 2 H), 3.10 (t, *J* = 2.3 Hz, 2 H, **2a**).

^{13}C NMR ($CDCl_3$, 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**).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{10}NO$: 124.0757; found: 124.0762.

1-Phenyl-1,5-dihydro-2*H*-pyrrol-2-one (1b)[10]

Following the general procedure on **6b** (648 mg, 5 mmol) and after purification by column chromatography on silica gel, compound **1b** was obtained as a beige solid; yield: 310 mg (39%); mp 90 °C; R_f = 0.46 (CH_2Cl_2/EtOAc 10:1).

IR (neat): 3080, 2906, 1683, 1500, 1429, 1371, 1210, 1143, 796, 754, 660 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.71 (m, 2 H), 7.37 (m, 2 H), 7.15 (m, 2 H), 6.24 (td, *J* = 6.0, 1.9 Hz, 1 H), 4.40 (t, *J* = 1.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.2, 142.6, 139.1, 129.1, 129.0, 124.2, 118.8, 53.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}NO$: 160.0757; found: 160.0759.

1-Benzyl-1,5-dihydro-2*H*-pyrrol-2-one (1c)[9b]

Following the general procedure on **6c** (2.14 g, 20 mmol) and after purification by column chromatography on silica gel, compound **1c** was obtained as a pale yellow solid; yield: 2.32 g (67%); mp 60 °C; R_f = 0.24 (EtOAc/cyclohexane 60:40).

IR (neat): 3089, 2923, 1699, 1668, 1450, 1404, 1341, 1242, 799, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.42–7.23 (m, 5 H), 7.09 (dt, *J* = 6.0, 1.8 Hz, 1 H), 6.25 (dt, *J* = 6.0, 1.8 Hz, 1 H), 4.67 (s, 2 H), 3.92 (t, *J* = 1.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4, 142.9, 137.3, 128.8, 127.9, 127.6, 52.3, 45.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO$: 174.0913; found: 174.0919.

(*S*)-1-(1-Phenylethyl)-1,5-dihydro-2*H*-pyrrol-2-one (1d)[11b]

Following the general procedure on **6d** (303 mg, 2.5 mmol) 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% yield (135 mg).

1d

R_f = 0.22 (EtOAc/cyclohexane 50:50); $[\alpha]_D^{20}$ –154.7 (*c* 1.2, $CHCl_3$).

IR (neat): 2978, 1685, 1658, 1446, 1239, 1220, 801, 748, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.19 (m, 5 H), 7.01 (dt, *J* = 5.9, 1.8 Hz, 1 H), 6.39 (dt, *J* = 5.9, 1.8 Hz, 1 H), 5.54 (q, *J* = 7.0 Hz, 1 H), 3.91 (dt, *J* = 20.5, 1.8 Hz, 1 H), 3.59 (dt, *J* = 20.5, 1.8 Hz, 1 H), 1.58 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.1, 143.1, 140.9, 128.6, 127.7, 127.5, 126.9, 48.9, 48.7, 17.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO$: 188.1070; found: 188.1073.

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

R_f = 0.62 (EtOAc/cyclohexane 50:50).

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.39–7.25 (m, 5 H), 6.39 (dt, *J* = 5.0, 2.0 Hz, 1 H), 5.47 (q, *J* = 7.1 Hz, 1 H), 5.28 (dt, *J* = 5.0, 2.4 Hz, 1 H), 3.12 (t, *J* = 2.2 Hz, 2 H), 1.61 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.5, 140.9, 130.2, 128.7, 127.6, 126.7, 104.6, 49.2, 37.8, 18.8.

1-[3-(3,4-Dimethoxyphenyl)propyl]-1,5-dihydro-2*H*-pyrrol-2-one (1e)[8b]

Following the general procedure on **6e** (4.35 g, 24 mmol) and after purification by column chromatography on silica gel, compound **1e** was obtained as a yellow oil; yield: 4.44 g (75%); R_f = 0.21 (EtOAc).

IR (neat): 2934, 1659, 1514, 1451, 1260, 1233, 1139, 1024, 800 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.02 (td, *J* = 6.0, 1.8 Hz, 1 H), 6.85–6.72 (m, 3 H), 6.18 (td, *J* = 6.0, 1.8 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.80 (t, *J* = 1.8 Hz, 2 H), 3.71 (t, *J* = 7.2 Hz, 2 H), 2.88 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 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.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1287; found: 248.1278.

Methyl (*S*)-6-{[(Benzyloxy)carbonyl]amino}-2-(2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoate (1f)

Following the general procedure on **6f** (32.1 g, 97 mmol) and after purification by column chromatography on silica gel, compound **1f** was obtained as a yellow oil; yield: 27.3 g (78%); R_f = 0.31 (EtOAc/cyclohexane 70:30); $[\alpha]_D^{20}$ +3.8 (*c* 1, CH_2Cl_2).

IR (neat): 3322, 2930, 2864, 1673, 1529, 1444, 1239, 1203, 802, 739, 697 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36 (m, 5 H), 7.15 (dt, *J* = 6.1 1.7 Hz, 1 H), 6.19 (dt, *J* = 6.1, 1.7 Hz, 1 H), 5.10 (s, 2 H), 4.99 (br t, 1 H, NH), 4.90 (dd, *J* = 10.8, 4.9 Hz, 1 H), 4.27 (d, *J* = 20.1 Hz, 1 H), 3.94 (d, *J* = 20.1 Hz, 1 H), 3.73 (s, 3 H), 3.19 (dd, *J* = 13.1, 6.7 Hz, 2 H), 1.96–2.13 (m, 1 H), 1.89–1.74 (m, 1 H), 1.58 (m, 2 H), 1.30 (m, 2 H).

^{13}C NMR ($CDCl_3$, 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.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_5$: 361.1758; found: 361.1756.

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

Following the general procedure on **6g** (2.16 g, 10 mmol) 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) yield.

1g

R_f = 0.27 (EtOAc/cyclohexane 50:50); $[\alpha]_D^{20}$ –36.1 (*c* 0.2, CH_2Cl_2).

IR (neat): 3029, 2952, 1739, 1682, 1662, 1436, 1241, 1207, 1168, 802, 748, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.19 (m, 5 H), 7.10 (dt, *J* = 6.1, 1.9 Hz, 1 H), 6.15 (dt, *J* = 6.1, 1.9 Hz, 1 H), 5.24 (dd, *J* = 10.5, 5.8 Hz, 1 H), 4.20 (dt, *J* = 19.8, 1.7 Hz, 1 H), 3.95 (dt, *J* = 19.8, 1.7 Hz, 1 H), 3.76 (s, 3 H), 3.45 (dd, *J* = 14.3, 5.8 Hz, 1 H), 3.13 (dd, *J* = 14.3 10.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 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.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_3$: 246.1125; found: 240.1124.

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

R_f = 0.50 (EtOAc/cyclohexane 50:50).

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.15 (m, 5 H), 6.57 (dt, *J* = 5.1, 2.1 Hz, 1 H), 5.29 (dq, *J* = 2.5, 0.5 Hz, 1 H), 5.12 (dd, *J* = 9.8, 5.8 Hz, 1 H), 3.75 (s, 3 H), 3.35 (dd, *J* = 14.2, 5.8 Hz, 1 H), 3.07 (dd, *J* = 14.2, 5.8 Hz, 1 H), 3.00 (t, *J* = 2.3 Hz, 1 H), 2.96 (t, *J* = 2.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 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.

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

Following the general procedure on **6h** (335 mg, 2 mmol) 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).

1h

R_f = 0.28 (EtOAc/cyclohexane 50:50); $[\alpha]_D^{20}$ –61.7 (*c* 1, CH_2Cl_2)

IR (neat): 2963, 2877, 1739, 1669, 1436, 1243, 1199, 1175, 803 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.14 (dt, *J* = 6.0, 1.8 Hz, 1 H), 6.15 (dt, *J* = 6.0, 1.8 Hz, 1 H), 4.56 (d, *J* = 10.2 Hz, 1 H), 4.33 (dt, *J* = 20.6, 1.7 Hz, 1 H), 3.99 (dt, *J* = 20.6, 1.7 Hz, 1 H), 3.68 (s, 3 H), 2.2 (m, 1 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.8, 171.6, 144.1, 126.9, 59.4, 51.9, 50.2, 29.3, 19.3, 19.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}NO_3$: 198.1125; found: 198.1126.

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

R_f = 0.57 (EtOAc/cyclohexane 50:50).

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.76 (dt, *J* = 4.6, 2.1 Hz, 1 H), 5.35 (q, *J* = 2.5 Hz, 1 H), 4.58 (d, *J* = 9.4 Hz, 1 H), 3.77 (s, 3 H), 3.13 (m, 2 H), 2.25 (m, 1 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.0, 171.2, 131.0, 104.0, 59.0, 52.1, 36.9, 30.4, 19.2, 18.8.

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

In an NMR tube, L-phenylalanine methyl ester hydrochloride (**6g**; 43 mg, 0.2 mmol) was dissolved in D_2O (0.6 mL). A few drops of aq 1 M HCl were added to adjust the pH to 1, followed by 2,5-dimethoxy-2,5-dihydrofuran (**5**; 25 µL, 0.2 mmol). After 10 min at 25 °C, the reaction was complete (see NMR spectra in Figures 2 and 3).

^1H NMR (D_2O, 300 MHz): δ = 7.28–7.23 (m, 3 H), 7.15–7.12 (m, 2 H), 6.00 (m, 3 H), 5.70 (m, 1 H), 4.70 (s, 2 H), 4.28 (dd, *J* = 7.5, 6.0 Hz, 1 H), 3.68 (s, 3 H), 3.22 (m, 1 H), 3.19 (s, 6 H, CH_3OH), 3.11 (m, 1 H).

^{13}C NMR (D_2O, 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 (CH_3OH), 35.5.

1-Allyl-5-methoxypyrrolidin-2-one (9a)[16b]

Following the general procedure on purified **1a** (190 mg, 1.54 mmol) after evaporation, compound **9a** was obtained as a pale yellow oil; yield: 160 mg (67%).

IR (neat): 2935, 1685, 1444, 1414, 1245, 1188, 1075, 884, 656 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.87–5.72 (m, 1 H), 5.30–5.19 (m, 2 H), 4.93 (dd, *J* = 6.2, 1.4 Hz, 1 H), 4.30 (dddd, *J* = 15.3, 4.6, 3.3, 1.7 Hz, 1 H), 3.63 (dddd, *J* = 15.3, 7.5, 2.0, 1.0 Hz, 1 H), 3.30 (s, 3 H), 2.56 (ddd, *J* = 17.2, 9.0, 9.0 Hz, 1 H), 2.38 (ddd, *J* = 17.2, 9.7, 3.1 Hz, 1 H), 2.26–2.11 (m, 1 H), 2.10–1.98 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.8, 132.4, 117.9, 89.4, 53.0, 42.8, 29.0, 23.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{14}NO_2$: 156.1025; found: 156.1018.

5-Methoxy-1-phenylpyrrolidin-2-one (9b)[20b]

Following the general procedure (except stirring for 22 h) on purified **1b** (111 mg, 0.7 mmol) and after purification by column chromatography on silica gel, compound **9c** was obtained as a pale yellow oil; yield: 102 mg (75%); R_f = 0.4 (CH_2Cl_2/MeOH 10:1).

IR (neat): 2935, 2828, 1698, 1497, 1394, 1293, 1193, 1067, 756, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.54 (m, 2 H), 7.40 (m, 2 H), 7.24 (m, 1 H), 5.34 (dd, *J* = 5.8, 0.8 Hz, 1 H), 3.30 (s, 3 H), 2.77 (ddd, *J* = 17.3, 9.3, 9.3 Hz, 1 H), 2.50 (ddd, *J* = 17.3, 9.5, 2.5 Hz, 1 H), 2.35–2.20 (m, 1 H), 2.20–2.09 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.5, 137.9, 129.0, 126.1, 123.2, 92.0, 53.6, 30.0, 24.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NO_2$: 192.1025; found: 192.1017.

1-Benzyl-5-methoxypyrrolidin-2-one (9c)[20]

Following the general procedure on crude **1c** (138 mg, 0.8 mmol) and after purification by column chromatography on silica gel, compound **9c** was obtained as a pale yellow oil; yield: 107 mg (65%); R_f = 0.65 (EtOAc).

IR (neat): 2933, 2828, 1691, 1442, 1417, 1244, 1171, 1073, 703 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.24 (m, 5 H), 4.96 (d, *J* = 14.7 Hz, 1 H), 4.74 (dd, *J* = 6.1, 1.5 Hz, 1 H), 4.03 (d, *J* = 14.7 Hz, 1 H), 3.23 (s, 3 H), 2.59 (ddd, *J* = 17.2, 8.8, 8.8 Hz, 1 H), 2.39 (ddd, *J* = 17.2, 9.5, 3.5 Hz, 1 H), 2.17–1.93 (m, 2 H).

^{13}C NMR ($CDCl_3$, 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]$^+$ calcd for $C_{12}H_{16}NO_2$: 206.1181; found: 2061187.

5-Methoxy-1-[(*S*)-1-phenylethyl]pyrrolidin-2-one (9d)[11b]

Following the general procedure on purified **1d** (280 mg, 1.5 mmol) and after purification by column chromatography on silica gel, compound **9d** was obtained as a yellow oil; yield: 243 mg (74%); two diastereoisomers (dr 33:67); R_f = 0.53 (major), 0.44 (minor) (EtOAc/cyclohexane 70:30).

IR (neat): 2935, 2828, 1691, 1462, 1425, 1244, 1182, 1078, 745 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.46–7.17 (m, 5 H), 5.35 (q, *J* = 7.2 Hz, 0.7 H, major), 5.12 (q, *J* = 7.2 Hz, 0.3 H, minor), 5.03 (dd, *J* = 6.2, 1.1 Hz, 0.3 H, minor), 4.46 (m, 0.7 H, major), 3.13 (s, 2 H, minor), 2.94 (s, 1 H, minor), 2.6–2.46 (m, 1 H), 2.22–2.36 (m, 1 H), 2.17–1.94 (m, 0.6 H, minor), 1.94–1.82 (m, 1.4 H, major), 1.65 (d, *J* = 7.2 Hz, 1 H, minor), 1.61 (d, *J* = 7.2 Hz, 2 H, major).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.0 (minor), 174.8 (major), 141.4 (minor), 139.9 (major), 128.6 (major), 127.7 (major + minor), 128.1 (minor), 127.4 (major), 127.2 (minor), 89.1 (major), 88.9 (minor), 52.6 (major), 52.1 (minor), 51.3 (minor), 50.5 (major), 29.5 (minor), 29.2 (major), 24.2 (minor), 24.0 (major), 18.1 (major), 17.6 (minor).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_2$: 220.1337; found: 220.1341.

Methyl (2*S*)-6-{[(Benzyloxy)carbonyl]amino}-2-(2-methoxy-5-oxopyrrolidin-1-yl)hexanoate (9f)

Following the general procedure on purified **1f** (6.62 g, 18.4 mmol) and after purification by column chromatography on silica gel, compound **9f** was obtained as a yellow oil; yield: 5.9 g (82%); two diastereoisomers (dr 53:47); R_f = 0.4 (EtOAc/cyclohexane 70:30).

IR (neat): 3339, 2948, 1693, 1243, 1075, 731, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37 (m, 5 H) 5.12 (m, 2 H), 4.88 (br d, 1 H, NH), 4.86 (br d, *J* = 5.4 Hz, 0.8 H), 4.69 (dd, *J* = 5.3, 10.0 Hz, 0.6 H), 4.49 (dd, *J* = 9.1, 6.1 Hz, 0.5 H), 3.78 (s, 1.4 H, minor), 3.71 (s, 1.6 H, major), 3.29 (s, 1.4 H, minor), 3.26 (s, 1.6 H, major), 3.19 (m, 2 H), 2.60 (m, 1 H), 2.43–2.28 (m, 1 H), 2.23–1.78 (m, 4 H), 1.66–1.26 (m, 4 H).

^{13}C NMR ($CDCl_3$, 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.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}NO_6Na$: 415.1840; found: 415.1838.

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

Following the general procedure on purified **1g** (1.54 g, 6.3 mmol) and after purification by column chromatography on silica gel, compound **9g** was obtained as a yellow oil; yield: 1.41 g (81%); two diastereoisomers dr 57:43; R_f = 0.3 (EtOAc/cyclohexane 40:60).

IR (neat): 2950, 1739, 1694, 1436, 1416, 1240, 1194, 1169, 1075, 749, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.18–7.36 (m, 5 H)), 4.92 (m, 0.83 H, minor), 4.50 (dd, *J* = 9.5, 6.5 Hz, 0.58 H, major), 4.41 (t, *J* = 3.7 Hz, 0.58 H, major), 3.75 (s, 1.7 H, major), 3.71 (s, 1.3 H, minor), 3.27–3.47 (m, 2 H), 3.22 (s, 1.7 H, major), 3.16 (s, 1.3 H, minor), 2.46–2.62 (m, 1 H), 2.17–2.35 (m, 1 H), 1.89–2.02 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.9 (minor), 24.0 (major), 28.7 minor), 28.8 (major), 34.1 (minor), 35.7 (major), 52.4 (minor), 52.5 (major), 52.5 (major), 53.7 (minor), 56.6 (major), 88.7 (minor), 90.6 (major), 126.7 (minor), 126.8 (major), 128.5, 128.9, 129.1, 136.8 (minor), 137.7 (major), 170.7 (major), 171.0 (minor), 174.9 (minor), 175.0 (major).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_4Na$: 300.1206; found: 300.1205.

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

Following the general procedure on purified **1h** (1.26 g, 6.4 mmol) and after purification by column chromatography on silica gel, compound **9h** was obtained as a yellow oil; yield: 1.08 g (70%); two diastereoisomers (dr 60:40); R_f = 0.32 (major), 0.41 (minor), (EtOAc/cyclohexane 50:50).

IR (neat): 2955, 2829, 1740, 1699, 1415, 1243, 1192, 1174, 1072 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): 4.81 (m, 0.6 H, major), 4.81 (m, 0.34 H, minor), 4.43 (d, *J* = 10.9 Hz, 0.34 H, minor), 4.31 (d, *J* = 9.4 Hz, 0.6 H, major), 3.71 (s, 1.1 H, minor), 3.68 (s, 1.9 H, major), 3.31 (s, 1.1 H, minor), 3.20 (s, 1.9 H, major), 2.60 (m, 1 H), 2.40–2.22 (m, 2 H), 2.09–2.00 (m, 2 H), 1.01 (d, *J* = 6.6 Hz, 1.9 H, major), 0.98 (d, *J* = 6.8 Hz, 1.1 H, minor), 0.96 (d, *J* = 6.8 Hz, 1.1 H, minor), 0.81 (d, *J* = 6.6 Hz, 1.9 H, major).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.9 (minor), 175.0 (major), 171.5 (minor), 170.8 (major), 90.3 (minor), 88.5 (major), 58.3 (major), 54.2 (major), 54.0 (minor), 52.0 (major), 51.8 (minor), 29.8 (minor), 28.3 (major and minor), 27.0 (major), 24.7 (minor), 24.6 (major), 19.8 (major), 19.7 (minor), 19.4 (minor), 18.6 (major).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}NO_4Na$: 252.1206; found: 252.1207.

5-Allyl-1-[(*S*)-1-phenylethyl]pyrrolidin-2-one (11d)[19,23a]

Following the general procedure on **9d** (110 mg, 0.5 mmol) and after purification by column chromatography on silica gel, compound **11d** was obtained as a colorless oil; yield: 90 mg (79%); two diastereoisomers (dr 77:23); R_f = 0.38 (EtOAc/cyclohexane 50:50).

IR (neat): 2974, 2935, 1675, 1411, 1260, 1026, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45–7.23 (m, 5 H), 5.70–5.38 (m, 2 H), 5.11–4.85 (m, 2 H), 3.79 (tt, *J* = 8.2, 3.2 Hz, 0.77 H, major), 3.34 (tt, *J* = 8.2, 3.1 Hz, 0.23 H, minor), 2.59–2.44 (m, 1 H), 2.41–2.27 (m, 1 H), 2.17–2.01 (m, 1 H), 1.98–1.85 (m, 1 H), 1.83–1.67 (m, 2 H), 1.66 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.4 (major), 175.3 (minor), 141.9 (major), 139.7 (minor), 133.3 (major), 133.2 (minor), 128.6 (minor), 128.4 (major), 127.6 (minor), 127.4 (major), 127.2 (major), 118.2 (major), 56.5 (minor), 56.2 (major), 50.6 (minor), 49.4 (major), 39.6 (minor), 38.8 (major), 30.3, 23.9 (major), 23.7 (minor), 18.3 (minor), 16.3 (major).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}NO$: 230.1545; found: 230.1548.

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

Following the general procedure on **9h** (115 mg, 0.5 mmol) and after purification by column chromatography on silica gel, compound **11h** was obtained as a colorless oil; yield: 102 mg (85%); two diastereoisomers (dr 70:30); R_f = 0.5 (EtOAc/cyclohexane 50:50).

IR (neat): 2965, 2875, 1739, 1686, 1412, 1252, 1203, 1008, 916 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.84–5.62 (m, 1 H), 5.21–5.10 (m, 2 H), 4.36 (d, *J* = 10.7 Hz, 0.3 H, minor), 4.10 (d, *J* = 10.2 Hz, 0.7 H, major), 3.74 (s, 2.1 H, major), 3.72 (s, 1.0 H, minor), 3.77–3.71 (m, 0.3 H, mi-

nor), 3.70–3.60 (m, 0.7 H, major), 2.70–2.60 (m, 0.7 H, major), 2.54–2.03 (m, 5.6 H), 1.92–1.76 (m, 1 H), 1.05 (d, *J* = 6.6 Hz, 0.9 H, minor), 1.04 (d, *J* = 6.6 Hz, 2.1 H, major), 0.96 (d, *J* = 6.6 Hz, 2.1 H, major), 0.88 (d, *J* = 6.6 Hz, 0.9 H, minor).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.0 (minor), 175.6 (major), 171.7 (minor), 170.5 (major), 133.4 (major), 133.3 (minor), 118.6 (minor), 118.5 (major), 61.6 (major), 59.8 (minor), 59.1 (major), 56.3 (minor), 51.9, 38.5 (major), 37.8 (minor), 29.6 (major), 29.5 (minor), 29.1 (major), 26.7 (minor), 24.2 (minor), 24.0 (major), 20.5 (major), 20.1 (minor), 19.3 (minor), 19.2 (major).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{22}NO_3$: 240.1594; found: 240.1596.

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

Following the general procedure on purified **1e** (124 mg, 0.5 mmol) and after purification by column chromatography on silica gel, compound **12** was obtained as a brown solid; yield: 72 mg (60%); mp 100–104 °C; R_f = 0.22 (EtOAc).

IR (neat): 2937, 1674, 1513, 1417, 1253, 1229, 1117, 1027, 1005, 861, 766 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.60 (s, 1 H), 4.76 (t, *J* = 7.5 Hz, 1 H), 4.33 (dd, *J* = 12.2, 5.1 Hz, 1 H), 3.90 (s, 3 H), 6.65 (s, 1 H), 3.89 (s, 3 H), 3.04 (ddd, *J* = 11.9, 11.9, 4.4 Hz, 1 H), 2.90 (ddd, *J* = 11.4, 11.4, 5.5 Hz, 1 H), 2.77–2.43 (m, 4 H), 1.86 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 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.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281; found: 248.1283.

(±)-Crispine A (13)[27]

Under an argon atmosphere, $LiAlH_4$ (50 mg, 1.3 mmol) was dissolved in anhyd THF (7 mL) and the solution cooled to 0 °C. Compound **12** (60 mg, 0.24 mmol) dissolved in anhyd THF (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 rt. Et_2O (3 mL) was added and the reaction was quenched by careful addition of sat. aq sodium potassium tartrate (0.5 mL). The mixture was stirred for a further 1 h before the addition of anhyd $MgSO_4$ 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 using 10:1.5 CH_2Cl_2/MeOH as eluent. Compound **13** was obtained as a white solid; yield: 42 mg (75%); mp 86 °C (Lit.[27] mp 88–89 °C); R_f = 0.5 (CH_2Cl_2/MeOH 10:1.5).

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

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.65 (s, 1 H), 6.61 (s, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.44 (t, *J* = 8.2 Hz, 1 H), 3.26–3.17 (m, 1 H), 3.17–2.99 (m, 2 H), 2.82–2.52 (m, 3 H), 2.42–2.29 (m, 1 H), 2.07–1.84 (m, 2 H), 1.84–1.68 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 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.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_2$: 234.1488; found: 234.1493.

Funding Information

Financial support of this work by Université de Paris (grant to Sébastien Thueillon).

Acknowledgment

The authors wish to thank Dr. Jean-François Betzer (ICSN, CNRS) for fruitful scientific discussions during the preparation of this manuscript.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707886.

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