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Cyclization of enaminones derived from *N*-phenacylpyrrolidin-2-ones to pyrrolizines under acidic conditions

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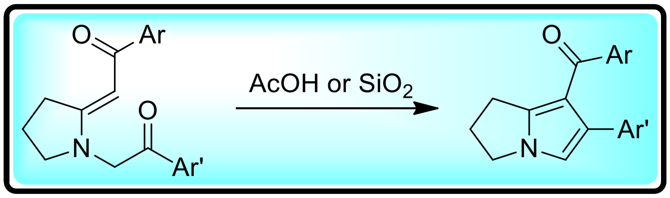
Abstract

Several *N*-phenacyl enaminones, prepared by Eschenmoser sulfide contraction between *N*-phenacylpyrrolidine-2-thiones and a range of substituted phenacyl halides, were transformed into 2,3-dihydro-1*H*-pyrrolizines when treated with acetic acid or silica gel. Yields of the bicyclic products were in the range 57–100% depending on the route followed. Some further reactions of the newly formed pyrrole rings are also reported.



Keywords: Enaminones, thiolactams, sulfide contraction, pyrrolizines, cyclization

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Introduction

We have previously reported mechanistic investigations into the synthesis of the phenyl-substituted 1,2,3,5,8,8a-hexahydroindolizine **1** as part of a preliminary study aimed at the synthesis of arylated indolizidine alkaloids such as (+)-ipalbidine (**2**) and (−)-septicine (**3**) (Figure 1).[1] Our intended strategy was based on the intermediacy of pyrrolidinone-derived enaminones (vinylogous amides) of type **4**, which we hoped to cyclize to $\Delta^{6,7}$-indolizidines either by C=C reduction to **5** followed by pinacol or McMurry coupling, or by Wittig reaction of **5** to form methylene precursors such as **6** for ring-closing metathesis.[2] Similar ring-closing approaches have been proposed by Honda and co-workers, and applied to the synthesis of (+)-ipalbidine.[3] In this article we report an unexpected formation of pyrrolizines during the preparation of **4**, and some further reactions of the products.

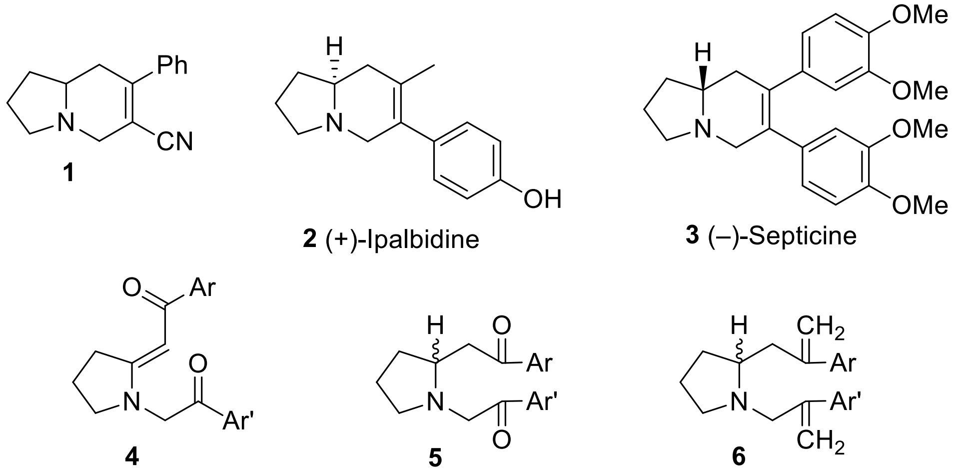
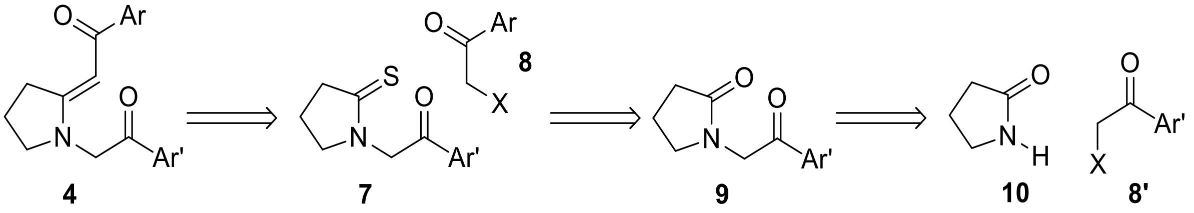


Figure 1. Synthetic and naturally occurring indolizidines **1-3**, and potential synthetic precursors **4**-**6**

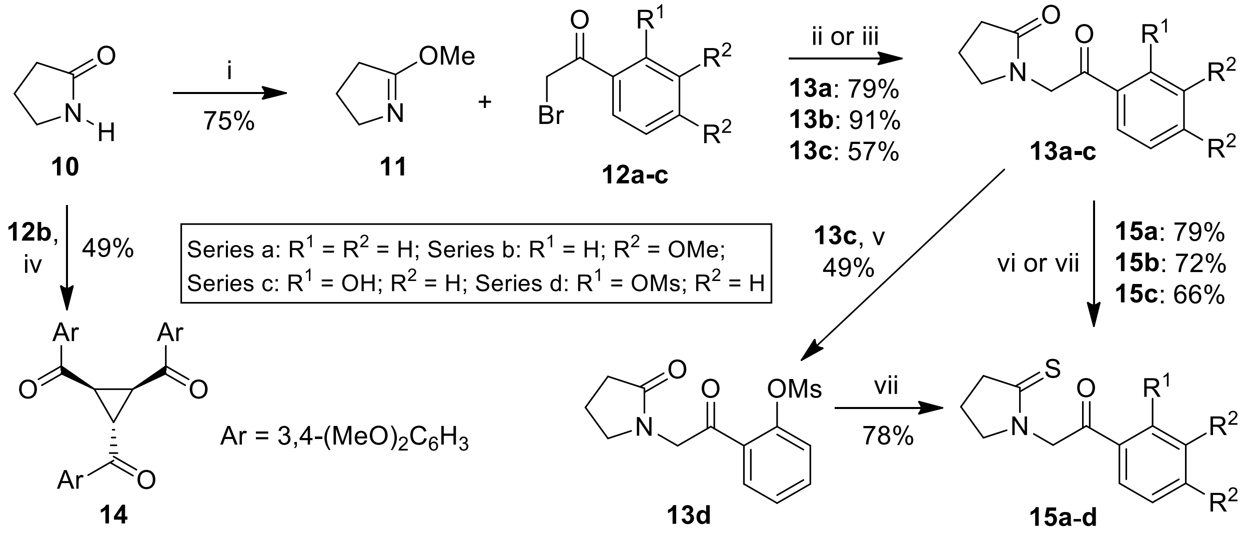
Results and Discussion

The strategy we planned for preparing the key enaminones **4** is shown in disconnection form in Scheme 1. Eschenmoser sulfide contraction,[4,5] a method we have used with much success in our routes to alkaloids and related nitrogen heterocycles,[6-10] was envisaged between pyrrolidine-2-thiones **7** and appropriately substituted phenacyl halides **8**. Intermediates **7** would themselves be made by thionation of the corresponding lactams **9**, which would in turn be prepared by N-alkylation of pyrrolidin-2-one (**10**) with phenacyl halides **8'**.



Scheme 1. Proposed disconnection scheme for the synthesis of enaminones **4** by sulfide contraction

Synthesis of the desired N-substituted lactams was effected by alkylation of the cyclic imidate **11**, prepared from pyrrolidin-2-one (**10**) and dimethyl sulfate,[11] with phenacyl bromide (**12a**), 3,4-dimethoxyphenacyl bromide (**12b**),[12] and 2-hydroxyphenacyl bromide (**12c**)[13] (Scheme 2). The products **13a-c** were obtained in yields of 79%, 91% and 57%, respectively. An alternative attempt to prepare **13b** by alkylating the anion of **10**, formed by reaction with sodium hydride or even potassium carbonate, with **12b** failed; the only isolable compound was *trans*-1,2,3-tris(3,4-dimethoxybenzoyl)cyclopropane (**14**), a known product from base-induced trimerization of **12b**.[14] A fourth lactam, the mesylate **13d**, was prepared in an unoptimized yield of 49% by treating the phenol **13c** with sodium hydride in tetrahydrofuran followed by methanesulfonyl chloride. The ensuing thionation of **13a** was effected by Curphey's method with phosphorus pentasulfide in the presence of hexamethyldisiloxane[15] to give **15a** (79%), while treating **13b**–**13d** with Lawesson's reagent[16] in toluene at 80 °C produced thiolactams **15b**–**15d** in more reproducible yields of 72%, 66% and 78%, respectively, after purification by column chromatography on silica gel. The yield of **15c** in particular was rather good in view of the presence of the free phenol, which was expected to present complications during the thionation.



Reagents and conditions: i) Me_2SO_4, 60 °C, 18 h (ref. 11); ii) **12a**, 60 °C, 20 h; iii) **12b,c**, DMF, 60-80 °C, 4-18 h ; iv) **10** + **12b**, K_2CO_3, Bu_4NBr, MeCN, rt, 24 h; v) **13c**, NaH, THF, rt, 30 min, then $MeSO_2Cl$, 35 min; vi) **13a**, P_4S_{10}, $(Me_3Si)_2O$, CH_2Cl_2, rt, 18 h; vii) **13b-d**, Lawesson's reagent, PhMe, 80 °C, 0.5-18 h.

Scheme 2. Synthesis of pyrrolidine-2-thiones **15a-d.**

The stage was now set for the synthesis of the desired enaminones by Eschenmoser sulfide contraction. The first phase of this process entails salt formation between the α-bromoketones **12** and thiones **15**. However, salt formation between phenacyl bromide (**12a**) and thione **15a** in acetonitrile was incomplete unless the concentration was kept relatively high (0.5–1.0 M). The subsequent extrusion of sulfur by dropwise addition of a solution of triethyl phosphite and triethylamine in acetonitrile over two hours followed by column chromatography was disappointing, affording the enaminone **16a** in a poor yield of 44% after column chromatography on silica gel (Scheme 3). Several unidentified by-products were also apparent, and it appeared that decomposition of **16a** occurred during chromatography. The sulfide contraction between the dimethoxy-substituted precursors **12b** and **16b** followed by careful chromatographic purification gave the enaminone **16b** in a better yield of 78%. The (*E*)-geometry of both **16a** and **16b** was inferred from the chemical shift of the ring hydrogen atoms at C-3 (*ca* δ 3.5), the downfield shift of *ca* 0.5 ppm relative to (*Z*)-enaminones resulting from anisotropic deshielding by the enaminone's carbonyl substituent.[4] In addition, the (*E*)-geometry of **16a** was confirmed by single-crystal X-ray diffraction (Figure 2a).

A clue to the poor yield of enaminone **16a** emerged after attempted reduction of the C=C bond in **16b** with hydrogen and platinum dioxide in acetic acid–methanol (3:1). The outcome was curious and altogether unforeseen: instead of the expected tertiary amine, the isolated product proved to be the 2,3-dihydro-1*H*-pyrrolizine **17b**, which was isolated in 83% yield! Moreover, simply dissolving the enaminone in acetic acid–methanol at room temperature in the absence of hydrogen and the catalyst brought about quantitative cyclization to the same pyrrolizine within 18 hours. Similar treatment of enaminone **16a** with acetic acid–methanol at room temperature afforded the analogous pyrrolizine **17a** (93%) after 24 hours. In a third example, *in situ* sulfide contraction between the mesylate **15d** and phenacyl iodide (**18**), prepared by Finkelstein exchange between bromide **12a** and sodium iodide in acetone,[17] followed immediately by heating the reaction mixture containing the crude enaminone intermediate **16d** (not characterized) with acetic acid–methanol at 45 °C gave the pyrrolizine **17d** in 57% yield.

The question then arose: could the poor yield of enaminone **16a** in the sulfide contraction be due to its loss by ready cyclization and aromatization on the acidic silica gel surface during chromatographic purification? After several trial reactions to test this hypothesis, it was found that adsorbing the crude reaction mixture from the sulfide contraction between **12a** and **15a** onto silica gel before heating the resulting powder at 90 °C for two hours prior to chromatography indeed produced pyrrolizine **17a** (69%). A further test involved a “mixed” reaction between phenacyl bromide (**12a**) and the 3,4-dimethoxyphenyl-substituted thione **15b**; heating the crude product from the Eschenmoser process on silica gel prior to chromatographic purification afforded pyrrolizine **19** in 66% yield. However, the *in situ* tandem sulfide contraction between phenacyl iodide (**18**) and the phenolic thiolactam **15c** followed by treatment of the crude product with silica gel failed, perhaps owing to incompatibility with the free phenol. The only isolable product was the unusual lactam **20** (27%), the structure and (*Z*)-geometry of which, and the presence of an intramolecular hydrogen bond between the phenol and ketone, were substantiated by X-ray crystallography (Figure 2b). Evidently, an ylide formed between **18** and triphenylphosphine effects Wittig reaction with the phenacyl carbonyl group, the resulting double bond then isomerizing into conjugation with nitrogen and the 2-hydroxyphenyl ring. Hydrolysis of the thione back to the carbonyl also occurs under the reaction conditions.

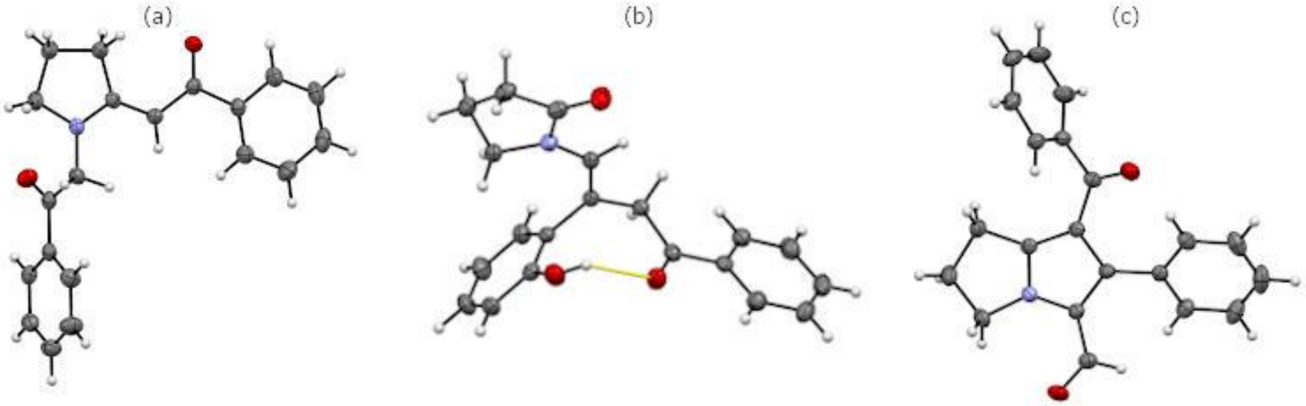
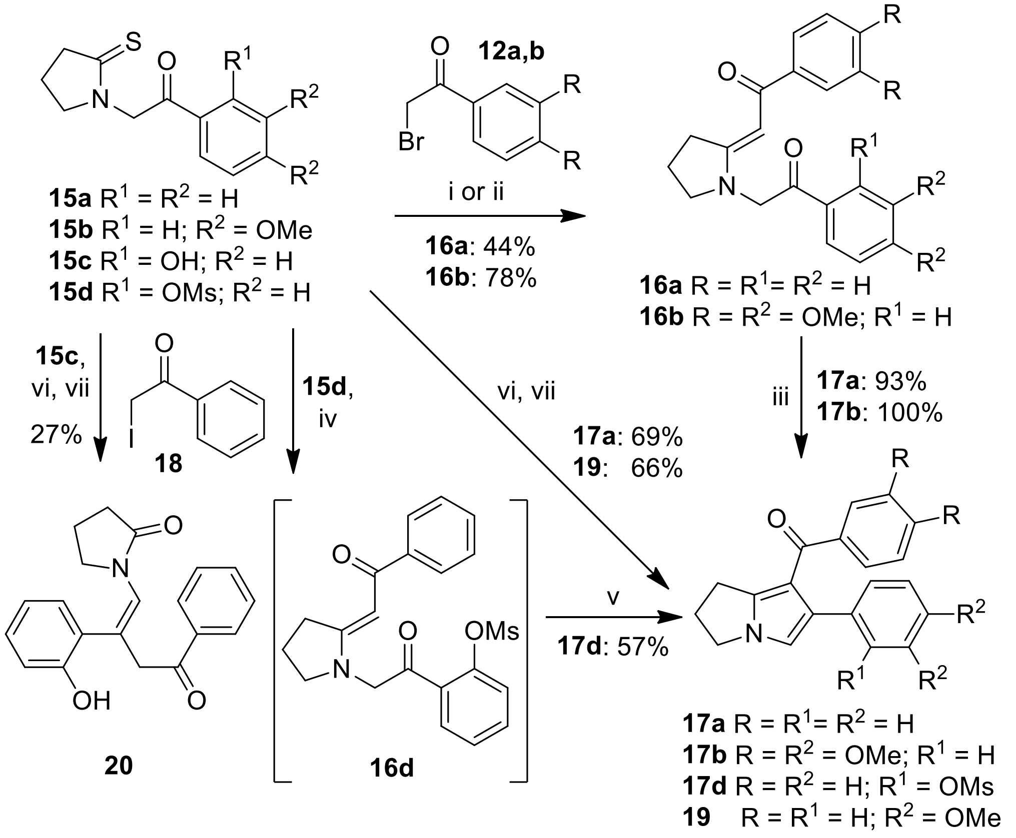


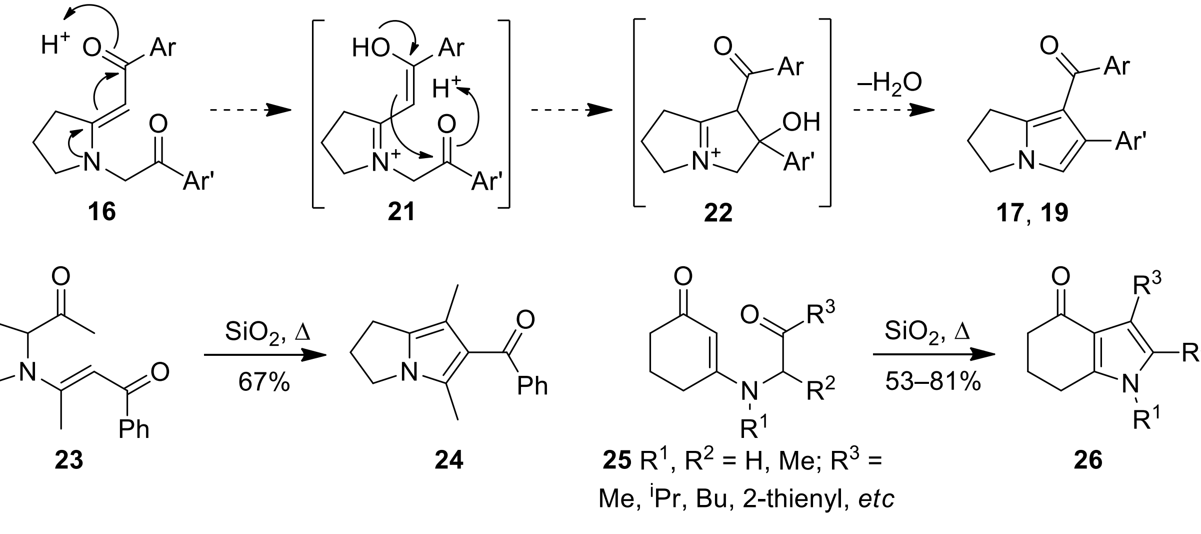
Figure 2. ORTEP diagrams of the crystal structures of: (a) **(***E***)**-2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]-1-phenylethanone (**16a**); (b) (*Z*)-1-[2-(2-hydroxyphenyl)-4-oxo-4-phenylbut-1-en-1-yl]pyrrolidin-2-one (**20**), showing the intramolecular hydrogen bond; (c) 7-benzoyl-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde (**32**). Thermal ellipsoids are at 50% probability.



Reagents and conditions: i) **12a** + **15a**, MeCN, rt, 24 h, then $P(OMe)_3$, NEt_3, rt, 30 min; ii) **12b** + **15b**, MeCN, 50 °C, 48 h, then $P(OMe)_3$, NEt_3, rt, 2 h; iii) AcOH-MeOH, rt, 18-24 h; iv) **15d** + **18**, MeCN, rt, 18 h, then $P(OMe)_3$, NEt_3, rt, 18 h; v) AcOH-MeOH, 45 °C, 18 h; vi) **15a,c** + **18**, MeCN, rt or reflux, 18 or 4 h, then PPh_3, NEt_3, MeCN, rt, 18h; vii) SiO_2, 90 °C, 1-2 h.

Scheme 3. Formation of pyrrolizines **17** and **19** via enaminones

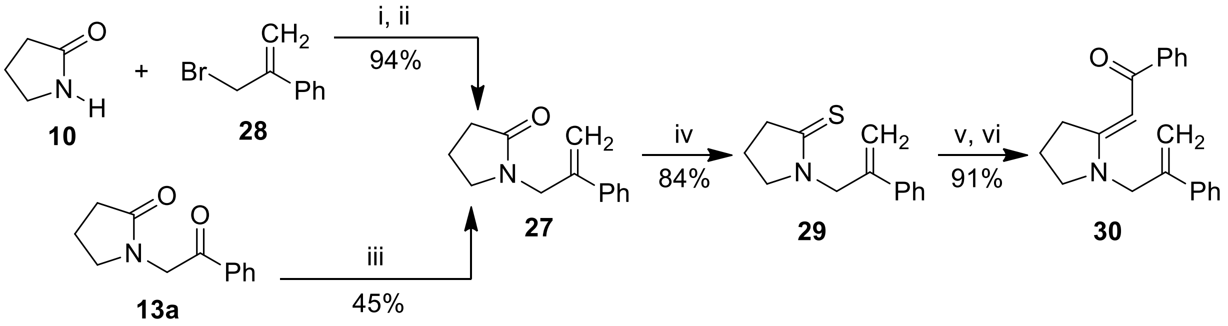
The formation of the pyrrolizines via enaminones under the acidic conditions can be rationalized as follows. After protonation of the enaminones **16**, the enolic carbon site in intermediates **21** reacts with the nearby ketone in a 5-*exo*-trig process, the resulting bicyclic intermediate **22** then undergoing aromatization by acid-induced elimination of water to form the pyrrole-containing products **17** and **19** (Scheme 4, upper line).



Scheme 4. Proposed mechanism for conversion of enaminones into pyrrolizines, and related literature examples.[18,19]

The silica-induced enaminone cyclizations are not without precedent. Calvo *et al.* showed that the vinylogous amide **23** as well as related vinylogous urethanes and vinylogous cyanamides cyclized to pyrrolizines such as **24** when heated with silica gel in chloroform or toluene (Scheme 4, lower line).[18] Related cyclizations of the enaminones **25** on silica gel to give 6,7-dihydro-1*H*-indol-4(5*H*)-ones **26** were also reported by these workers.[19] All of these cyclizations, like ours, can be viewed as variants of the classic Knorr synthesis of pyrroles.[20-22]

For comparison we also investigated the reaction sequence with a 2-phenylallyl substituent replacing phenacyl on nitrogen. The requisite lactam **27** was prepared in 94% yield by alkylating the anion of pyrrolidin-2-one (**10**) with 2-phenylallyl bromide (**28**)[23] (Scheme 5). The alternative preparation of **27** by Wittig methylenation of the corresponding ketone **13a** was less satisfactory, affording only a 45% yield of the desired product. Thionation of **27** with Lawesson's reagent gave a good yield of thione **29** (84%). Salt formation with phenacyl bromide (**12a**) in acetonitrile followed by sulfide contraction with triphenylphosphine and triethylamine afforded enaminone **30** (91%) which, as expected, was stable and showed no signs of cyclization. We have previously reported a synthesis of **30** and confirmed its (*E*)-geometry by X-ray crystallography.[24]

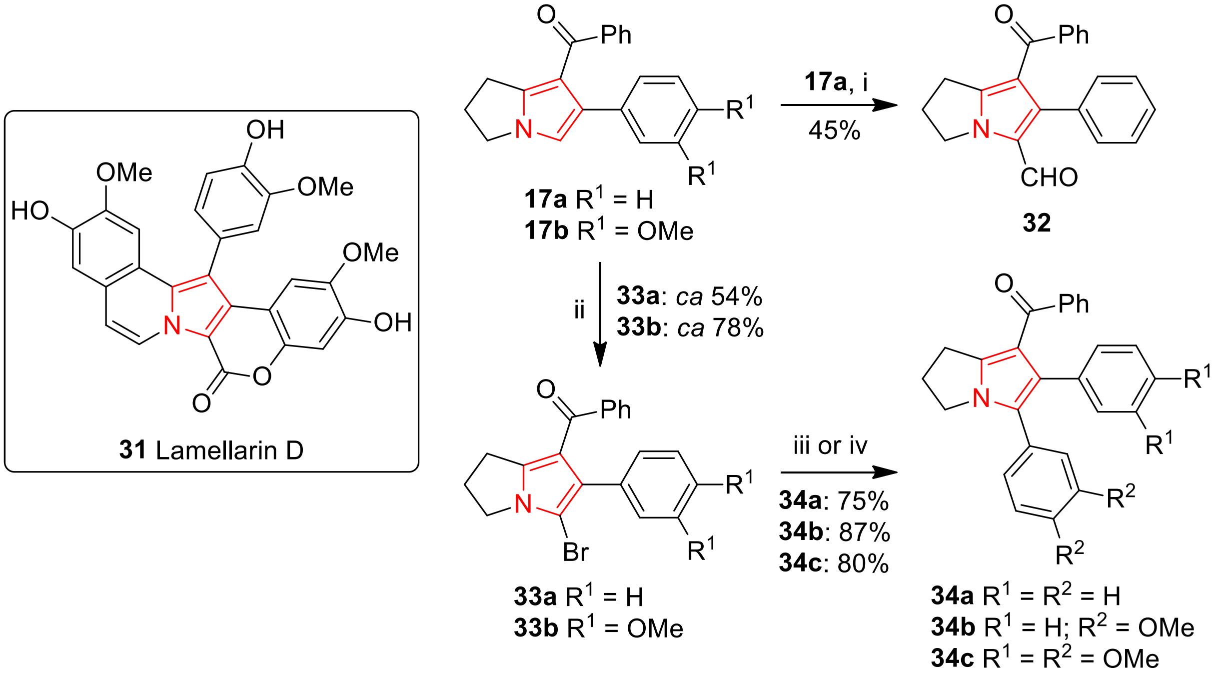


Reagents and conditions: i) **10**, NaH, DMF, 60°C, 1 h; ii) add **28**, DMF, 0 °C, then 60 °C, 3 h; iii) $Ph_3P=CH_2$, THF, –10 °C, 0.5 h, then rt, 40 h; iv) Lawesson's reagent, PhMe, 60 °C, 15 h; v) $PhCOCH_2Br$ (**12a**), MeCN, rt, 3 h; vi) add PPh_3, NEt_3, rt, 18 h.

Scheme 5. Synthesis of *N*-(2-phenylallyl) enaminone **30**

A final set of investigations was prompted by our continuing interest[7,25] in the synthesis of lamellarins, an important group of marine alkaloids possessing an impressive range of biological activities.[26] Typical alkaloids such as lamellarin D (**31**) contain a fully substituted pyrrole core. We were interested to ascertain whether, and how readily, the unsubstituted site on the pyrrole ring in pyrrolizines **17** could be made to bear a substituent. We found that a carbonyl group could be introduced into precursor **17a** by Vilsmaier–Haack formylation with *N*,*N*-dimethylformamide to produce aldehyde **32**, although in only 45% yield. Its structure, which incidentally also confirms the pyrrolizine core, was verified by X-ray crystallography (Figure 2c). Of greater interest was the introduction of aromatic rings, since arylation of bromopyrroles by Suzuki–Miyaura coupling with arylboronic acids is a common feature in many syntheses of lamellarins.[26–29] We found that both **17a** and **17b** underwent bromination with *N*-bromosuccinimide in tetrahydrofuran, although the products **33a** and **33b** were so unstable that they had to be used in the subsequent Suzuki–Miyaura couplings as soon as they were prepared. Characterization of the labile bromides by NMR spectroscopy and HRMS was nonetheless possible. The palladium-mediated coupling of unpurified **33a** with phenylboronic acid afforded the 5,6-diaryl-

7-benzoylpyrrolizine **34a** in an overall yield of 75%, while coupling of both **33a** and **33b** with 3,4-dimethoxyphenylboronic acid gave the expected products **34b** and **34c** in overall yields of 87% and 80%, respectively. These successful aryl coupling reactions serve as useful models for our continuing researches into the synthesis of lamellarins and related natural products.



Reagents and conditions: i) $POCl_3$, DMF, CH_2Cl_2, rt, 1 h; ii) NBS, THF, rt, 20 min-1 h; iii) **33a**, $PhB(OH)_2$, $PPh_3)_4Pd$ (10 mol%), Na_2CO_3, EtOH:H_2O:DME (1:1:1), reflux, 18 h; iv) **33a** or **33b**, 3,4-$(MeO)_2C_6H_3B(OH)_2$, $(PPh_3)_4Pd$ (10 mol%), Na_2CO_3, EtOH:H_2O:DME (1:1:1), reflux, 1 h.

Scheme 6. Further transformation of pyrrolizines **17a** and **17b**

Conclusions

We have shown in this article that several *N*-phenacyl vinylogous amides, either isolated or prepared *in situ*, underwent an unexpected cyclization into 2,3-dihydro-1*H*-pyrrolizines under acidic conditions. There is synthetic potential in this transformation, since pyrrolizines are well represented both among naturally occurring alkaloids[30,31] and in compounds of pharmaceutical interest.[32,33] Analogous cyclizations of enaminones derived from *N*-(ethoxycarbonylmethyl)pyrrolidin-2-one and related lactams are currently underway in our laboratories, and will be reported in due course.

Experimental Section

General. All reactions, unless otherwise stated, were carried out under argon, and reaction vessels were dried either in an oven or flame-dried under vacuum. Tetrahydrofuran and diethyl ether were distilled under nitrogen gas from sodium wire with benzophenone as an indicator. Toluene was distilled from sodium lumps. Dichloromethane, *N,N*-dimethylformamide and acetonitrile were distilled from calcium hydride. Commercially available chemicals were used as received. Room temperature refers to ambient laboratory temperatures of 18–25 °C.

Solvents used for chromatographic purposes were distilled before use. Conventional column chromatography was performed on Merck silica-gel (particle size 0.063–0.200 mm), and flash column chromatography on

Merck silica-gel (particle size 0.04–0.063 mm). Thin layer chromatography was performed on Merck silica-gel 60 F_{254} coated on aluminum sheets, and compounds were visualized under UV light (254 nm) or by dipping the plates into a basic $KMnO_4$ staining solution. Melting points were measured on a Reichart micro hotstage apparatus.

^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker Avance I 300 MHz spectrometer at frequencies of 300 MHz for ^{1}H spectra and 75 MHz for ^{13}C spectra. Chemical shifts (δ) recorded in $CDCl_3$ solution are reported as parts per million (ppm) downfield from Me_4Si as internal reference for ^{1}H NMR spectra, and relative to the central signal for $CDCl_3$ at 77.16 ppm for ^{13}C NMR spectra. *J* values are given in Hz. Infra-red spectra were recorded on a Bruker Vector-22 Fourier Transform spectrometer or on a Bruker Tensor 27 Fourier Transform spectrometer with a diamond ATR attachment. High-resolution mass spectra were recorded on VG70 MS (Mass spectrum CC Pyramid data system), VG70 SEQ (VG 11-205J or Marc II data system) or DFS High Resolution Magnetic Sector mass spectrometers.

Crystal structure solution and refinement: A Bruker SMART 1K CCD area diffractometer was used to measure the Intensity data for compound **16a**, while intensity data for compounds **20** and **32** were collected on a Bruker APEX 2 CCD area detector diffractometer. Mo graphite-monochromated Kα radiation (50 kV, 30 mA) was used in both diffractometers. The collection method involved ω scans of width 0.5°. Data reduction was carried out using the program SAINT+ (SAINT V6.02A[34] for the SMART 1K, and V8.34A[35] for the APEX 2). The structures were solved by direct methods using SHELXS-1997,[36] with non-hydrogen atoms refined isotropically at first, followed by anisotropic refinement using full-matrix least-squares calculations based on F^2 using SHELXL-2018/3.[37] All hydrogen atoms were first located in the difference-Fourier map then positioned geometrically and allowed to ride on their respective parent atoms. Software used in this work was as follows: Data collection: SMART-NT[38] and APEX2;[39] cell refinement and data reduction: SAINT+;[34,35] program suites used to solve and refine structures: SHELX-1997[36] and SHELX-2014;[37] software used to prepare material for publication: Olex2,[40] PLATON,[41] and Mercury.[42] CCDC-1995286, 1995287 and 1995288 contain the supplementary crystallographic data for compounds **16a**, **20** and **32**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1-(2-Oxo-2-phenylethyl)pyrrolidin-2-one (**13a**). This compound was prepared by a known procedure.[43] A mixture of 5-methoxy-3,4-dihydro-2*H*-pyrrole (**11**)[11] (6.00 g, 60.5 mmol) and phenacyl bromide (**12a**) (8.00 g, 40.2 mmol) was stirred under N_2 at 60 °C for 20 h. The resulting crude product mixture was dissolved in EtOAc (100 mL) and washed with aq. NaOH (2 M, 100 mL), H_2O (100 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to afford a red oil. Column chromatography with EtOAc afforded 1-(2-oxo-2-phenylethyl)pyrrolidin-2-one (**13a**) (6.49 g, 31.9 mmol, 79%) as a white solid, mp 69–71 °C (lit.,[43] 70–71 °C); R_f (EtOAc) 0.29. IR (ATR, $ν_{max}$, cm^{-1}): 3062 (w), 2917 (w), 1698 (s), 1681 (s), 1597 (w), 1580 (w), 1385 (w), 1290 (m), 1228 (m), 1075 (w). ^{1}H NMR (300 MHz, $CDCl_3$): $δ_H$ 7.95 (dd, *J* 7.9, 1.5 Hz, 2H), 7.60 (apparent tt, *J* 7.5, 1.5 Hz, 1H), 7.48 (apparent t, *J* 7.5 Hz, 2H), 4.73 (s, 2H), 3.50 (t, *J* 7.2 Hz, 2H), 2.47 (t, *J* 8.1 Hz, 2H), 2.11 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $δ_C$ 193.9, 175.8, 135.0, 133.8, 128.9, 128.0, 49.1, 47.9, 30.5, 18.1. HRMS-EI *m/z* $[M]^+$ calcd for $C_{12}H_{13}NO_2^+$ 203.0941, found 203.0915.

1-[2-(3,4-Dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13b**). 5-Methoxy-3,4-dihydro-2*H*-pyrrole (**11**)[11] (1.19 g, 12.0 mmol) and 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (**12b**)[12] (2.59 g, 10.0 mmol) were stirred in dry DMF (5 mL) under N_2 at 80 °C for 4 h. The solvent was evaporated *in vacuo* to afford a red oil, column chromatography of which with 10% MeOH in EtOAc afforded 1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13b**) (2.40 g, 9.11 mmol, 91%) as a yellow gum, R_f (10% MeOH–EtOAc) 0.44. IR (ATR, $ν_{max}$, cm^{-1}): 3085 (w), 2955 (w), 2928 (w), 2841 (w), 1686 (s), 1670 (s), 1587 (m), 1516 (m), 1261 (s), 1152

9s), 1018 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.62 (dd, *J* 8.4, 2.1 Hz, 1H), 7.52 (d, *J* 1.8 Hz, 1H), 6.91 (d, *J* 8.4 Hz, 1H), 4.69 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.50 (t, *J* 7.2 Hz, 2H), 2.48 (t, *J* 8.1 Hz, 2H), 2.11 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 192.7, 175.8, 154.0, 149.3, 128.2, 122.9, 110.4, 110.3, 56.3, 56.2, 48.9, 48.0, 30.6, 18.2. HRMS-EI *m/z* [M]$^+$ calcd for $C_{14}H_{17}NO_4^+$ 263.1152, found 263.1130.

1-[2-(2-Hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13c**). The above procedure was repeated with 5-methoxy-3,4-dihydro-2*H*-pyrrole (**11**) (4.15 g, 41.9 mmol) and 2-bromo-1-(2-hydroxyphenyl)ethanone (**12c**)[13] (6.00 g, 27.9 mmol) in dry DMF (5 mL) at 60 °C for 18 h. Work-up and chromatography as described above afforded 1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13c**) (3.51 g, 16.0 mmol, 57%) as a pink solid that turned white on standing in air, mp 78–79 °C, R_f (80% EtOAc/hexane) 0.30. IR (ATR, ν_{max}, cm^{-1}): 2945 (w), 2863 (w), 1675 (m), 1646 (s), 1598 (s), 1457 (s), 1227 (m), 1161 (m), 1026 (m), 764 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 11.76 (s, 1H, OH), 7.75 (dd, *J* 8.0, 1.2 Hz, 1H), 7.50 (ddd, *J* 8.8, 7.7, 1.7 Hz, 1H), 7.00 (dd, *J* 8.1, 1.8 Hz, 1H), 6.92 (apparent t, *J* 7.6 Hz, 1H), 4.76 (s, 2H), 3.51 (t, *J* 7.0 Hz, 2H), 2.49 (t, *J* 8.4 Hz, 2H), 2.14 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 199.4, 175.9, 162.5, 137.0, 129.2, 119.4, 118.8, 118.0, 48.6, 48.1, 30.4, 18.2. HRMS-EI *m/z* [M]$^+$ calcd for $C_{12}H_{13}NO_3^+$ 219.0890, found 219.0891.

2-[2-(2-Oxopyrrolidin-1-yl)acetyl]phenyl methanesulfonate (**13d**). NaH (60% dispersion in oil, 226 mg, 5.65 mmol) was added to a solution of 1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13c**) (1.03 g, 4.70 mmol) in dry THF (25 mL). The mixture was stirred under Ar for 30 min. Methanesulfonyl chloride (0.647 g, 0.44 mL, 5.65 mmol) was added, and stirring was continued for 35 min. H_2O (1 mL) was added and stirring was continued for 5 min. The solvent was evaporated and the residue was extracted with EtOAc (25 mL), which was washed with H_2O (25 mL) and brine (25 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to give an orange gum, flash chromatography of which with EtOAc afforded 2-[2-(2-oxopyrrolidin-1-yl)acetyl]phenyl methanesulfonate (**13d**) (687 mg, 2.31 mmol, 49%) as an orange gum, R_f (EtOAc) 0.30. IR (ATR, ν_{max}, cm^{-1}): 2938 (w), 1670 (m, br), 1604 (m), 1291 (s), 1198 (m), 1157 (s), 971 (m), 862 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.77 (dd, *J* 7.7, 1.6 Hz, 1H), 7.59 (ddd, *J* 9.0, 7.3, 1.9 Hz, 1H), 7.50–7.40 (m, 2H), 4.63 (s, 2H), 3.52 (t, *J* 7.2 Hz, 2H), 3.29 (s, 3H), 2.46 (t, *J* 8.1 Hz, 2H), 2.11 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 195.0, 176.0, 146.2, 133.8, 131.0, 130.1, 127.7, 123.9, 51.9, 48.0, 38.5, 30.4, 18.3. HRMS-EI *m/z* [M]$^+$ calcd for $C_{13}H_{15}NO_5S^+$ requires 297.0665, found 297.0666.

[2,3-Bis-(3,4-dimethoxybenzoyl)cyclopropyl](3,4-dimethoxyphenyl)methanone (**14**). Bu_4NBr (7.57 g, 23.5 mmol) and K_2CO_3 (8.11 g, 58.7 mmol) were added to a solution of 2-pyrrolidinone (**10**) (500 mg, 5.88 mmol) in dry MeCN (30 mL). 2-Bromo-1-(3,4-dimethoxyphenyl)-1-ethanone (**12b**) (2.00 g, 7.72 mmol) was added and the solution was vigorously stirred for 24 h under an atmosphere of N_2. The heterogeneous reaction mixture was filtered and the filter pad was washed with EtOAc (50 mL). The filtrate was taken up into additional EtOAc (150 mL) and washed with H_2O (3 × 50 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to give a red crystalline mass. This solid was washed repeatedly with a minimum volume of EtOAc to afford [2,3-bis(3,4-dimethoxybenzoyl)cyclopropyl](3,4-dimethoxy-phenyl)methanone (**14**) (700 mg, 1.31 mmol, 51%) as an amorphous powder, mp 200–201 °C (lit.,[14] 202–204 °C). IR (NaCl, ν_{max}, cm^{-1}): 2938 (w), 2841 (w), 1656 (s), 1584 (s), 1512 (s), 1260 (s), 1242 (s), 1144 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.94 (dd, *J* 8.4, 1.9 Hz, 1H), 7.72 (dd, *J* 8.4, 1.9 Hz, 2H), 7.67 (d, *J* 1.9 Hz, 1H), 7.52 (d, *J* 1.9 Hz, 2H), 6.96 (d, *J* 8.5 Hz, 1H), 6.86 (d, *J* 8.4 Hz, 2H), 4.17 (t, *J* 5.6 Hz, 1H), 3.98 and 3.97 (2 × s, 6H), 3.92 (s, 6H), 3.87 (s, 6H), 3.69 (d, *J* 5.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 194.7, 191.9, 154.2, 153.8, 149.3, 149.2, 130.1, 130.0, 124.2, 123.5, 110.5, 110.4, 110.2, 56.3, 56.2, 56.1, 36.0, 30.3. ^{1}H NMR signals are reported at 60 MHz in the literature as 6.8-8.1 (9H, m) and 4.3–3.7 (21H, m, with three strong singlets for -OCH_3).[14]

1-Phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone (**15a**). P_4S_{10} (3.34 g, 7.51 mmol) was added to a stirring solution of 1-(2-oxo-2-phenylethyl)pyrrolidin-2-one (**13a**) (8.00 g, 39.4 mmol) in dry CH_2Cl_2 (50 mL) under N_2 at room temperature. $(Me_3Si)_2O$ (15.0 mL, 11.5 g, 70.8 mmol) in dry CH_2Cl_2 (50 mL) was added, and stirring was continued for 18 h. EtOAc (50 mL) was then added, and the reaction mixture was filtered through a pad of SiO_2 (150 g, 20 g SiO_2/mmol P_4S_{10}) with EtOAc (1 L). The filtrate was evaporated to give a yellow gum, column chromatography of which with 40% EtOAc/hexane afforded 1-phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone (**15a**) (6.87 g, 31.3 mmol, 79%) as a white solid, mp 64–65 °C, R_f (50% EtOAc/hexane) 0.49. IR (ATR, ν_{max}, cm^{-1}): 3053 (w), 2965 (w), 2899 (w), 1689 (s), 1597 (m), 1581 (w), 1461 (s), 1230 (s), 1218 (s), 1127 (s), 1076 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.00 (dd, *J* 8.4, 1.2, Hz, 2H), 7.63 (apparent t, *J* 7.4 Hz, 1H), 7.50 (apparent t, *J* 7.6 Hz, 2H), 5.29 (s, 2H), 3.85 (t, *J* 7.3 Hz, 2H), 3.14 (t, *J* 7.9 Hz, 2H), 2.17 (quintet, *J* 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 203.7, 192.3, 135.0, 134.2, 129.1, 128.2, 55.8, 54.1, 44.4, 20.0. HRMS-EI *m/z* $[M]^+$ calcd for $C_{12}H_{13}NOS^+$ 219.0712, found 219.0716.

1-(3,4-Dimethoxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone (**15b**). 1-[2-(3,4-Dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13b**) (495 mg, 1.88 mmol) was stirred under N_2 with Lawesson's reagent (421 mg, 1.04 mmol) in dry toluene (10 mL) at 80 °C for 30 min. Evaporation of the solvent gave a yellow gum, column chromatography of which with 50% EtOAc/hexane afforded 1-(3,4-dimethoxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone (**15b**) (377 mg, 1.35 mmol, 72%) as a pale yellow solid, mp 97–98 °C, R_f (50% EtOAc/hexane) 0.26. IR (ATR, ν_{max}, cm^{-1}): 2942 (w), 2903 (w), 1679 (s), 1597 (m), 1587 (m), 1510 (s), 1258 (s), 1237 (s), 1144 (s), 1124 (s, C=S), 1060 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.65 (dd, *J* 8.4, 2.0 Hz, 1H), 7.53 (d, *J* 1.9 Hz, 1H), 6.92 (d, *J* 8.4 Hz, 1H), 5.24 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.83 (t, *J* 7.3 Hz, 2H), 3.12 (t, *J* 7.9 Hz, 2H), 2.15 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 203.3, 190.9, 154.1, 149.3, 128.0, 122.9, 110.4, 110.2, 56.2, 56.1, 55.7, 53.8, 44.4, 19.8. HRMS-EI *m/z* $[M]^+$ calcd for $C_{14}H_{17}NO_3S^+$ 279.0924, found 279.0948.

1-(2-Hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone (**15c**). 1-[2-(2-Hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13c**) (517 mg, 2.36 mmol) was stirred under Ar with Lawesson's reagent (485 mg, 1.20 mmol) in dry toluene (10 mL) at 80 °C for 4 h. Evaporation of the solvent afforded an orange gum, flash chromatography of which with 30% EtOAc/hexane afforded 1-(2-hydroxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone (**15c**) (368 mg, 1.56 mmol, 66%) as a yellow solid, mp 85–86 °C (sublimation noted at 75 °C), R_f (30% EtOAc/hexane) 0.26. IR (ATR, ν_{max}, cm^{-1}): 3053 (w, br), 2982 (w), 2943 (w), 2912 (w), 1643 (s), 1615 (m), 1576 (m), 1511 (s), 1236 (s), 1198 (s), 1155 (s), 1020 (m), 756 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 11.66 (s, 1H, OH), 7.78 (dd, *J* 8.1, 1.4 Hz, 1H), 7.53 (ddd, *J* 8.7, 7.2, 1.7 Hz, 1H), 7.02 (dd, *J* 8.5, 1.2 Hz, 1H), 6.96 (ddd, *J* 8.3, 7.2, 1.2 Hz, 1H), 5.32 (s, 2H), 3.85 (t, *J* 7.3 Hz, 2H), 3.16 (t, *J* 7.9 Hz, 2H), 2.19 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 204.2, 197.5, 162.5, 137.4, 129.1, 119.6, 118.9, 118.0, 55.9, 53.4, 44.4, 20.0. HRMS-EI *m/z* $[M]^+$ calcd for $C_{12}H_{13}NO_2S^+$ 235.0662, found 235.0663.

2-[2-(2-Thioxopyrrolidin-1-yl)acetyl]phenyl methanesulfonate (**15d**). 2-[2-(2-Oxopyrrolidin-1-yl)acetyl]phenyl methanesulfonate (**13d**) (1.33 g, 4.47 mmol) was stirred under Ar with Lawesson's reagent (938 mg, 2.32 mmol) in dry toluene (50 mL) at 80 °C for 18 h. The solvent was evaporated to give an orange gum, column chromatography of which with 40% EtOAc/hexane afforded 2-[2-(2-thioxopyrrolidin-1-yl)acetyl]phenyl methanesulfonate (**15d**) (1.09 g, 3.48 mmol, 78%) as an orange gum, R_f (40% EtOAc/hexane) 0.26. IR (ATR, ν_{max}, cm^{-1}): 2994 (w), 2956 (w), 2919 (w), 1689 (m), 1672 (w), 1603 (m), 1572 (m), 1297 (s), 1170 (s), 1155 (s), 1059 (m), 860 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.91 (dd, *J* 7.6, 1.5 Hz, 1H), 7.61 (ddd, *J* 8.8, 7.2, 1.8 Hz, 1H), 7.50–7.40 (m, 2H), 5.16 (s, 2H), 3.87 (t, *J* 7.3 Hz, 2H), 3.29 (s, 3H), 3.11 (t, *J* 7.9 Hz, 2H), 2.17 (acetone overlapping with quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 203.7, 192.7, 146.2, 134.0, 130.9, 130.4, 127.7, 123.7, 56.7, 55.8, 44.2, 38.5, 20.0.

(*E*)-2-[1-(2-Oxo-2-phenylethyl)pyrrolidin-2-ylidene]-1-phenylethanone (**16a**). 1-Phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone (**15a**) (658 mg, 3.00 mmol) was added to a stirring solution of phenacyl bromide (**12a**) (597 mg, 3.00 mmol) in dry MeCN (5 mL) under N_2. After 24 h, $P(OEt)_3$ (0.57 mL, *ca* 550 mg, *ca* 3.31 mmol) and Et_3N

(0.47 mL, *ca* 330 mg, *ca* 3.26 mmol) were added. After 30 min the reaction mixture was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (20 mL). The organic extract was dried over Na_2SO_4, filtered and evaporated to give an orange gum, column chromatography of which with 50% EtOAc/hexane afforded (*E*)-2-[1-(2-oxo-2-phenylethyl)pyrrolidin-2-ylidene]-1-phenylethanone (**16a**) (400 mg, 1.31 mmol, 44%) as a yellow solid, mp 102–104 °C (acetone). The compound was unstable to chromatography on silica gel. R_f (50% EtOAc/hexane) 0.49. IR (ATR, ν_{max}, cm^{-1}): 3074 (w), 2962 (w), 2886 (w), 1686 (m), 1609 (m), 1594 (m), 1477 (br s), 1215 (s), 1019 (m), 759 (s). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.99 (dd, *J* 8.4, 1.4 Hz, 2H), 7.76 (dd, *J* 8.4, 1.7 Hz, 2H), 7.66 (apparent tt, *J* 7.4, 1.5 Hz, 1H), 7.54 (apparent t, *J* 7.5 Hz, 2H), 7.41–7.28 (m, 3H), 5.57 (s, 1H), 4.77 (s, 2H), 3.56 (t, *J* 7.3 Hz, 2H), 3.50 (t, *J* 7.8 Hz, 2H), 2.13 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 192.55, 192.52 (superimposed), 167.9, 142.0, 135.0, 134.3, 130.5, 129.2, 128.11, 128.05, 127.4, 87.1, 53.9, 52.7, 33.7, 21.4. HRMS-EI *m/z* $[M]^+$ calcd for $C_{20}H_{19}NO_2^+$ 305.1410, found 305.1390. X-ray crystal structure details of compound **16a (**CCDC-1995286): crystallized from acetone, formula: $C_{20}H_{19}NO_2$, *M* 305.36, color of crystal: colorless, plates, crystal size 0.40 × 0.34 × 0.04 mm^3, *a* 10.1009(5) Å, *b* 18.6845(10) Å, *c* 8.9120(4) Å, β 111.537(3)°, *V* 1564.53(14) $Å^3$, ρ_{calc} 1.296 Mg/m^3, μ 0.083 mm^{-1}, *F*(000) 648, *Z* = 4, monoclinic, space group $P2_1/c$, *T*=173(2) K, 10302 reflections collected, 3072 independent reflections, θ_{max} 25.992°, 208 refined parameters, maximum residual electron density 0.192 and −0.212 e.$Å^{-3}$. R_1 0.0403, wR_2 0.0994.

(*E*)-1-(3,4-Dimethoxyphenyl)-2-{1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}ethanone (**16b**). 1-(3,4-Dimethoxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone (**15b**) (200 mg, 0.72 mmol) was added to a stirring solution of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (**12b**) (197 mg, 0.76 mmol) in dry MeCN (5 mL) under N_2 at room temperature. After 2 h the reaction mixture was heated at 50 °C for 48 h. The reaction was allowed to cool to room temperature. $P(OEt)_3$ (0.14 mL, *ca* 131 mg, *ca* 0.79 mmol) and Et_3N (0.11 mL, *ca* 80 mg, *ca* 0.79 mmol) were added. After 2 h of additional stirring the reaction mixture was poured into EtOAc (50 mL) and washed with H_2O (2 × 25 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a yellow oil, column chromatography of which with EtOAc afforded (*E*)-1-(3,4-dimethoxyphenyl)-2-{1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}ethanone (**16b**) (240 mg, 0.56 mmol, 78%) as a yellow gum, R_f (EtOAc) 0.20. IR (ATR, ν_{max}, cm^{-1}): 2937 (w), 2837 (w), 1703 (m), 1610 (m), 1582 (m), 1511 (s), 1261 (s), 1018 (s). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.62 (dd, *J* 8.4, 2.0 Hz, 1H), 7.54 (d, *J* 1.9 Hz, 1H), 7.48 (d, *J* 1.9 Hz, 1H), 7.32 (dd, *J* 8.4, 1.9 Hz, 1H), 6.94 (d, *J* 8.4 Hz, 1H), 6.76 (d, *J* 8.4 Hz, 1H), 5.60 (s, 1H), 4.72 (s, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.56 (t, *J* 7.2 Hz, 2H), 3.49 (t, *J* 7.8 Hz, 2H), 2.12 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 191.3, 187.0, 167.5, 154.1, 151.2, 149.6, 148.8, 134.9, 128.3, 122.5, 120.5, 110.6, 110.2, 110.2, 109.9, 86.6, 56.3, 56.2, 56.04, 55.95, 53.9, 52.3, 33.6, 21.4. HRMS-EI *m/z* $[M]^+$ calcd for $C_{24}H_{27}NO_6^+$ 425.1833, found 425.1818.

Phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone (**17a**). **Method 1.** (***E***)-2-[1-(2-Oxo-2-phenylethyl)pyrrolidin-2-ylidene]-1-phenylethanone (**16a**) (214 mg, 0.70 mmol) was added to a solution of AcOH (5 mL) containing MeOH (2 mL) and stirred under N_2 for 24 h. The solvent was evaporated and the gum was extracted with EtOAc (25 mL). The organic extract was washed with a saturated solution of $NaHCO_3$ (2 × 25 mL) and H_2O (25 mL), then dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (50% EtOAc/hexane) afforded phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone (**17a**) (187 mg, 0.65 mmol, 93%) as a pale yellow gum, R_f (50% EtOAc/hexane) 0.60. IR (ATR, ν_{max}, cm^{-1}): 3058 (w), 3029 (w), 2964 (w), 1709 (m), 1630 (s), 1578 (m), 1371 (m), 1317 (m), 1272 (m), 1026 (w), 908 (s), 728 (s), 696 (s). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.63 (dd, *J* 8.3, 1.4 Hz, 2H), 7.33 (apparent tt, *J* 7.5, 1.5 Hz, 1H), 7.26–7.17 (m, 4H), 7.18–7.03 (m, 3H), 6.69 (s, 1H), 3.96 (t, *J* 7.2 Hz, 2H), 2.79 (t, *J* 7.4 Hz, 2H), 2.43 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 192.3, 145.6, 140.2, 135.6, 131.14, 131.08, 129.2, 128.7, 127.84, 127.75, 125.9, 114.44, 114.35, 47.0, 26.9, 26.3. HRMS-EI *m/z* $[M]^+$ calcd for $C_{20}H_{17}NO^+$ 287.1305, found 287.1305.

Phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone (**17a**). **Method 2.** A solution of phenacyl iodide[17] (**18**) (5.63 g, 22.9 mmol) and 1-phenyl-2-(2-thioxopyrrolidin-1-yl)ethanone (**15a**) (3.35 g, 15.3 mmol) in Et_2O (25 mL) was heated at reflux temperature under Ar for 18 hours. The solvent was decanted and the yellow solid that remained was rinsed with dry Et_2O (3 × 25 mL) to remove excess phenacyl iodide. MeCN (25 mL) was added, and the heterogeneous solution was stirred under Ar. A solution of PPh_3 (4.40 g, 16.8 mmol) and Et_3N (4.29 mL, *ca* 3.09 g, *ca* 30.5 mmol) in MeCN (25 mL) was added dropwise, and stirring was continued for 18 h. The solvent was evaporated, and the resulting orange gum was extracted into EtOAc (100 mL). The organic extract was washed with H_2O (50 mL) and brine (2 × 50 mL), dried over Na_2SO_4 and filtered. Silica gel (30 g) was added, and the reaction mixture was heated at 90 °C while the solvent was slowly removed on a rotary evaporator. When a free-flowing powder was obtained, stirring was continued for an additional 2 h at 90 °C. The powder was transferred to a glass-sintered filter funnel and washed with acetone (200 mL). The filtrate was evaporated to give an orange gum, column chromatography of which with 30% EtOAc/hexane afforded phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone (**17a**) (3.01 g, 10.5 mmol, 69%) as a yellow gum. The spectroscopic data matched those given above.

(3,4-Dimethoxyphenyl)[6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl]methanone (**17b**). **Method 1.** (*E*)-1-(3,4-Dimethoxyphenyl)-2-{1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}ethanone (**16b**) (435 mg, 1.02 mmol) was added to degassed solution of AcOH (6 mL) containing MeOH (2 mL) and PtO_2 (13 mg). The solution was hydrogenated at atmospheric pressure and room temperature for 7 h. The reaction mixture was filtered through a Celite pad and the pad was rinsed with additional AcOH (15 mL). The solvent was evaporated to give a brown gum which was extracted into CH_2Cl_2 (20 mL). The extract was washed with a saturated solution of $NaHCO_3$ (3 × 20 mL), dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (5% MeOH/ EtOAc) afforded (3,4-dimethoxyphenyl)[6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl]methanone (**17b**) (347 mg, 0.85 mmol, 83%) as a yellow gum, R_f (10% MeOH/EtOAc) 0.66. IR (ATR, ν_{max}, cm^{-1}): 2937 (w), 2866 (w), 1704 (m), 1651 (m), 1515 (s), 1267 (s), 1021 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.37 (dd, *J* 1.9, 8.3 Hz, 1H), 7.27 (d, *J* 1.2 Hz, 1H), 6.84 (dd, *J* 8.3, 1.9 Hz, 1H), 6.74–6.67 (m, 4H), 4.03 (t, *J* 7.2 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 2.97 (t, *J* 7.4 Hz, 2H), 2.52 (quintet, *J* 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 191.4, 152.1, 148.5, 148.3, 147.5, 145.2, 132.7, 130.5, 128.9, 124.0, 120.3, 114.4, 113.5, 112.8, 112.5, 111.1, 109.9, 56.03, 56.00, 55.9, 55.8, 47.1, 27.0, 26.2. HRMS-EI *m/z* [M]$^+$ calcd for $C_{24}H_{25}NO_5^+$ 407.1727, found 407.1733.

(3,4-Dimethoxyphenyl)[6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl]methanone (**17b**). **Method 2.** A solution of (*E*)-1-(3,4-dimethoxyphenyl)-2-{1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]pyrrolidin-2-ylidene}ethanone (**16b**) (49 mg, 0.12 mmol) in degassed AcOH (2 mL) containing MeOH (1 mL) was stirred at room temperature under Ar for 18 h. The reaction mixture was filtered through a Celite pad, which was then rinsed with additional AcOH (15 mL). The solvent was evaporated to give a brown gum, which was extracted into CH_2Cl_2 (20 mL). The extract was washed with a saturated solution of $NaHCO_3$ (3 × 20 mL), dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (5% MeOH/EtOAc) afforded (3,4-dimethoxyphenyl)[6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl]methanone (**17b**) (49 mg, 0.12 mmol, *ca* 100%) as a yellow gum. The spectroscopic data matched those reported above.

2-(7-Benzoyl-2,3-dihydro-1*H*-pyrrolizin-6-yl)phenyl methanesulfonate (**17d**). A solution of 2-[2-(2-thioxopyrrolidin-1-yl)acetyl]phenyl methanesulfonate (**15d**) (1.047 g, 3.34 mmol) and phenacyl iodide (846 mg, 3.44 mmol) in dry MeCN (10 mL) was stirred at room temperature under Ar for 18 h. A solution of $P(OEt)_3$ (0.63 mL, *ca* 610 mg, *ca* 3.67 mmol) and Et_3N (0.94 mL, *ca* 676 mg, *ca* 6.68 mmol) in MeCN (10 mL) was added dropwise and stirring was continued for 18 h. The solvent was evaporated and the residue was extracted with EtOAc (50 mL). The extract was washed with H_2O (3 × 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to give an orange gum. The gum was added to a solution of AcOH (25 mL) in MeOH (25 mL) and heated at 45 °C for 18 h. The solvent was evaporated and the residue was extracted with EtOAc (50 mL). The extract was washed successively with a saturated solution of $NaHCO_3$ (50 mL), H_2O (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to give an orange gum. Column chromatography (50% EtOAc/hexane) afforded 2-(7-benzoyl-2,3-dihydro-1*H*-pyrrolizin-6-yl)phenyl methanesulfonate (**17d**) (731 mg, 1.92 mmol, 57%) as a brown gum, R_f (60% EtOAc/hexane) 0.50. IR (ATR, ν_{max}, cm^{-1}): 2961 (w), 2921 (w), 1709 (m), 1623 (m), 1356 (s), 1157 (s), 1031 (m). ^1H NMR (300 MHz, $CDCl_3$): δ_H δ 7.67 (apparent dt, *J* 6.9, 1.5 Hz, 2H), 7.39 (apparent t, *J* 7.3 Hz, 1H), 7.34–7.24 (m, 3H), 7.24–7.14 (m, 3H), 6.80 (s, 1H), 4.05 (t, *J* 7.1 Hz, 2H), 2.86 (s, 3H), 2.79 (t, *J* 7.3 Hz, 2H), 2.45 (quintet, *J* 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 192.0, 146.4, 144.7, 139.9, 131.8, 131.4, 129.6, 129.1, 127.91, 127.85, 127.1, 124.5, 122.7, 116.1, 115.4, 47.2, 37.7, 27.1, 26.3. HRMS-ESI *m/z* $[M + Na]^+$ calcd for $C_{21}H_{19}NO_4SNa^+$ 404.0927 found 404.0924.

[6-(3,4-Dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**19**). A solution of 1-(3,4-dimethoxyphenyl)-2-(2-thioxopyrrolidin-1-yl)ethanone (**15b**) (645 mg, 2.31 mmol) and phenacyl iodide (1.137 g, 4.62 mmol) in MeCN (1.00 mL) was stirred at room temperature under Ar for 4 h. The reaction mixture was cooled to 0°C and a solution of PPh_3 (1.21 g, 4.61 mmol) and Et_3N (0.65 mL, *ca* 468 mg, 4.62 mmol) in MeCN (5 mL) was added dropwise. Stirring was continued for 18 h at room temperature. The solvent was evaporated and the residue was extracted with EtOAc (50 mL). The extract was washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4 and filtered. Silica gel (8 g) was added, and the reaction mixture was heated at 90 °C while the solvent was slowly removed on a rotary evaporator. When a free-flowing powder was obtained, stirring was continued for an additional 1 h. The powder was transferred to a glass-sintered filter funnel and washed with acetone (100 mL). The filtrate was evaporated to give an orange gum. column chromatography of which with 40% EtOAc/hexane afforded [6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**19**) (527 mg, 1.52 mmol, 66%) as an orange gum, R_f (40% EtOAc/hexane) 0.29. IR (ATR, ν_{max}, cm^{-1}): 3058 (w), 2936 (w), 2835 (w), 1704 (m), 1627 (s), 1597 (s), 1447 (s), 1248 (s), 1023 (s). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.63 (d, *J* 7.4 Hz, 2H), 7.33 (apparent t, *J* 7.1 Hz, 1H), 7.21 (apparent t, *J* 7.5 Hz, 2H), 6.84 (dd, *J* 8.2, 2.0 Hz, 1H), 6.71 and 6.69 (overlapping d, *J* 8.1 Hz, and s, 3H), 4.01 (t, *J* 7.1 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 2.87 (t, *J* 7.3 Hz, 2H), 2.48 (quintet, *J* 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 192.5, 148.2, 147.4, 145.8, 140.3, 131.2, 130.8, 129.2, 128.6, 127.8, 120.5, 114.4, 113.9, 112.8, 110.9, 55.9, 55.7, 47.1, 26.9, 26.4. HRMS-EI *m/z* $[M]^+$ calcd for $C_{22}H_{21}NO_3^+$ 347.1516, found 347.1518.

(*Z*)-1-[2-(2-Hydroxyphenyl)-4-oxo-4-phenylbut-1-en-1-yl]pyrrolidin-2-one (**20**). A solution of 1-[2-(2-hydroxyphenyl)-2-oxoethyl]pyrrolidin-2-one (**13c**) (850 mg, 3.61 mmol) in dry Et_2O (25 mL) was stirred under Ar at room temperature. A solution of phenacyl iodide (1.334 g, 5.42 mmol) in Et_2O (25 mL) was added and the reaction mixture was heated at reflux for 48 h, then cooled to room temperature. A solution of PPh_3 (1.52 g, 5.80 mmol) and Et_3N (1.01 mL, *ca* 731 mg, *ca* 7.22 mmol) in dry MeCN (25 mL) was added dropwise, and stirring was continued for 4 h. The solvents were evaporated, and the residue was extracted with EtOAc (50 mL). The extract was washed with H_2O (50 mL) and brine (25 mL), dried over Na_2SO_4, filtered and evaporated to give a red gum. Flash chromatography (40% EtOAc/hexane to 60% EtOAc/hexane) afforded an orange powder. The crude product was dissolved in toluene (25 mL) containing silica gel (2.73 g) and heated at reflux under Dean–Stark conditions for 90 min. The reaction mixture was filtered through a glass sintered funnel and the silica gel was rinsed with acetone (3 × 10 mL). The combined filtrate was evaporated to give an orange gum. Flash chromatography (40% EtOAc/hexane) afforded impure (*Z*)-1-[2-(2-hydroxyphenyl)-4-oxo-4-phenylbut-1-en-1-yl]pyrrolidin-2-one (**20**) (317 mg, 0.99 mmol, 27%) as an orange gum that slowly formed crystals on standing, R_f (40% EtOAc/hexane) 0.50. IR (ATR, ν_{max}, cm^{-1}): 3333 (w, br, OH), 2979 (w), 2981 (w), 1692 (s), 1675 (s), 1658 (s), 1598 (m), 1574 (m), 1488 (m), 1120 (s), 744 (s). ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.16

(br s, 1H, OH), 7.93 (d, *J* 7.3 Hz, 2H), 7.55 (apparent t, *J* 7.4 Hz, 1H), 7.42 (apparent t, *J* 7.6 Hz, 2H), 7.22–7.14 (m, 1H), 7.03 (dd, *J* 1.5, 7.6 Hz, 1H), 7.00 (s, 1H), 6.92 (d, *J* 7.6 Hz, 1H), 6.86 (apparent t, *J* 7.5 Hz, 1H), 4.10 (s, 2H), 3.08 (br s, 2H), 2.33 (t, *J* 8.2 Hz, 2H), 1.80 (quintet, *J* 7.6 Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 200.7, 174.9, 154.5, 135.5, 133.8, 130.2, 129.4, 128.6, 128.2, 126.7, 126.1, 119.7, 116.7, 110.2, 48.1, 45.9, 30.0, 18.0. LRMS *m/z* (%) 303 (100), 248 (10), 246 (56), 232 (52), 220 (24), 176 (6), 115 (4). HRMS-ESI *m/z* [M + Na]$^+$ calcd for $C_{20}H_{19}NO_3Na^+$ 344.1257, found 344.1262. X-ray crystal structure details of compound **20** (CCDC-1995287): formula: $C_{20}H_{19}NO_3$, *M* 321.36, color of crystal: colorless, needles, crystal size 0.43 × 0.24 × 0.20 mm^3, *a* 8.2094(2) Å, *b* 8.2445(2) Å, *c* 12.1999(3) Å, α 98.692(2)°, β 90.277(2)°, γ 103.958(1)°, *V* 791.40(3) Å^3, ρ_{calc} 1.349 g/m^3, μ 0.091 mm^{-1}, *F*(000) 340, *Z* = 2, triclinic, space group *P*-1, *T* 173(2) K, 17171 reflections collected, 3819 independent reflections, θ_{max} 27.999°, 221 refined parameters, maximum residual electron density 0.274 and −0.208 e.Å^{-3}. R_1 0.0410, wR_2 0.1120.

1-(2-Phenyl-2-propenyl)pyrrolidin-2-one (**27**). **Method 1.** NaH (60% dispersion in oil, 0.96 g, 24.0 mmol) was added to a stirring solution of pyrrolidin-2-one (**10**) (1.70 g, 20.0 mmol) in dry DMF (50 mL) under Ar. The solution was warmed to 60 °C and stirred for a further 1 h. The solution was cooled to 0 °C and 2-phenylallyl bromide (**28**)[23] (4.73 g, 24.0 mmol) in dry DMF (10 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and then heated at 60 °C for 3 h. The solvent was evaporated and the residue was taken up into EtOAc (100 mL) and washed with H_2O (4 × 50 mL) and brine (50 mL). The organic extract was dried over MgSO$_4$, filtered and evaporated to give a yellow oil. Column chromatography (80% EtOAc/hexane) afforded 1-(2-phenyl-2-propenyl)pyrrolidin-2-one (**27**) (3.78 g, 18.8 mmol, 94%) as a pale-yellow oil, R_f (80% EtOAc/hexane) 0.25. IR (ATR, ν_{max}, cm^{-1}): 3030 (w), 2917 (w), 1658 (br, s), 1576 (m), 1494 (m), 1463 (m), 1446 (m), 1310 (m), 1286 (m), 1070 (m). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.49–7.41 (m, 2H), 7.37–7.23 (m, 3H), 5.51 (s, 1H), 5.19 (d, *J* 0.9 Hz, 1H), 4.35 (s, 2H), 3.21 (t, *J* 7.1 Hz, 2H), 2.32 (t, *J* 8.1 Hz, 2H), 1.87 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 174.8, 143.1, 140.0, 128.5, 128.1, 126.1, 114.9, 46.45, 46.42, 30.9, 17.7. HRMS-EI *m/z* [M]$^+$ calcd for $C_{13}H_{15}NO^+$ 211.1148, found 201.1152.

1-(2-Phenyl-2-propenyl)pyrrolidin-2-one (**27**). **Method 2.** *n*-BuLi (1.6 M in hexanes, 1.84 mL, 2.94 mmol) was added to a stirred solution of methyltriphenylphosphonium bromide (1.07 g, 3.00 mmol) in dry THF (20 mL) under Ar at −10 °C. After 10 min the cooling bath was removed and stirring was continued at room temperature for 1 h. The reaction mixture was re-cooled to −10 °C and 1-(2-oxo-2-phenylethyl)pyrrolidin-2-one (**13a**) (500 mg, 2.46 mmol) in THF (5 mL) was added dropwise. The resulting mixture was stirred at −10 °C for 30 min and at room temperature for 40 h. H_2O (50 mL) was added, and the mixture was extracted with EtOAc (150 mL). The organic extract was dried over MgSO$_4$, filtered and evaporated to give a red oil, column chromatography of which with 80% EtOAc/hexane afforded 1-(2-phenyl-2-propenyl)pyrrolidin-2-one (**27**) (222 mg, 1.10 mmol, 45%) as a yellow oil. The spectroscopic data matched those reported above.

1-(2-Phenyl-2-propenyl)pyrrolidine-2-thione (**29**). 1-(2-Phenyl-2-propenyl)pyrrolidin-2-one (**27**) (3.00 g, 14.9 mmol) was stirred under Ar with Lawesson's reagent (3.14 g, 7.76 mmol) in dry toluene (50 mL) at 60 °C for 15 h. Evaporation of the solvent gave a yellow gum, column chromatography of which with 20% EtOAc/hexane afforded 1-(2-phenylprop-2-en-1-yl)pyrrolidine-2-thione (**29**) (2.73 g, 12.6 mmol, 84%) as a pale-yellow oil, R_f (20% EtOAc/hexane) 0.23. IR (ATR, ν_{max}, cm^{-1}): 3055 (w), 2916 (w), 1599 (w), 1574 (w), 1496 (br, s), 1464 (m), 1448 (m), 1235 (m), 1119 (m), 1028 (m). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.45 (dd, *J* 7.0, 1.5 Hz, 2H), 7.39–7.24 (m, 3H), 5.58 (s, 1H), 5.24 (s, 1H), 4.86 (s, 2H), 3.53 (t, *J* 7.3 Hz, 2H), 2.97 (t, *J* 7.9 Hz, 2H), 1.89 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C 201.8, 142.0, 137.4, 128.6, 128.3, 126.0, 115.8, 53.7, 51.6, 44.8, 19.5. HRMS-EI *m/z* [M]$^+$ calcd for $C_{13}H_{15}NS^+$ 217.0920, found 217.0923.

(*E*)-1-Phenyl-2-[1-(2-phenyl-2-propenyl)pyrrolidin-2-ylidene]ethanone (**30**). 1-(2-Phenylprop-2-en-1-yl)pyrrolidine-2-thione (**29**) (4.27 g, 19.6 mmol) was added to a stirring solution of phenacyl bromide (**12a**)

(4.30 g, 21.6 mmol) in dry MeCN (20 mL) under Ar. The gum that formed was briefly warmed to homogenize the solution, thereafter stirring was continued at room temperature for 3 h. A solution of PPh_3 (5.66 g, 21.6 mmol) and Et_3N (3.31 mL, 2.38 g, 23.5 mmol) in dry MeCN (20 mL) was added dropwise and stirring was continued for 18 h. The solvent was evaporated and the residue was taken up into EtOAc (200 mL). This was washed with H_2O (3 × 100 mL) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated to give an orange gum. Column chromatography (40% EtOAc/hexane) afforded (*E*)-1-phenyl-2-[1-(2-phenyl-2-propenyl)pyrrolidin-2-ylidene]ethanone (**30**) (5.42 g, 17.9 mmol, 91%) as a yellow solid, mp 62–63 °C, R_f (40% EtOAc/hexane) 0.30. IR (ATR, ν_{max}, cm^{-1}): 2888 (w), 1611 (m), 1596 (m), 1575 (m), 1530 (br, s), 1469 (s), 1289 (m), 1086 (m). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.87 (dd, *J* 7.5, 1.8 Hz, 2H), 7.47–7.27 (m, 8H), 5.84 (s, 1H), 5.52 (s, 1H), 5.16 (s, 1H), 4.33 (s, 2H), 3.44 and 3.42 (overlapping t, *J ca* 7.5 Hz, 4H), 2.00 (quintet, *J* 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 188.1, 167.4, 142.1, 141.0, 138.7, 130.5, 128.8, 128.4, 128.1, 127.4, 126.1, 114.2, 87.2, 52.8, 50.7, 33.9, 21.2. HRMS-EI *m/z* $[M]^+$ calcd for $C_{21}H_{21}NO^+$ 303.1618, found 303.1618.

7-Benzoyl-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde (**32**). Phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone (**17a**) (1.923 g, 6.69 mmol) was added to a solution of DMF (0.66 mL, 616 mg, 8.43 mmol) in CH_2Cl_2 (10 mL) and stirred at room temperature under N_2. $POCl_3$ (0.78 mL, 1.293 g, 8.43 mmol) was cautiously added from a syringe, and stirring was continued for an additional 1 h. Crushed ice was added, and after 5 min the deep-red solution was neutralized with a saturated solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc (50 mL), and the extract was passed through a short silica gel pad to remove most of the red color. The pad was rinsed with additional EtOAc (100 mL), and the combined organic extract was evaporated to give a brown gum. Column chromatography (40% EtOAc/hexane) afforded 7-benzoyl-6-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde (**32**) (0.948 g, 3.01 mmol, 45%) as a brown gum, R_f (40% EtOAc/hexane) 0.50. The gum was crystallized by slow evaporation from CH_2Cl_2/hexane mixtures to afford a brown solid, mp 97–98 °C (CH_2Cl_2/hexane). IR (ATR, ν_{max}, cm^{-1}): 3057 (w), 3026 (w), 2965 (w), 2832 (w), 1643 (s), 1598 (m), 1579 (m), 1464 (s), 1276 (m), 1218 (m), 1032 (w), 970 (s). ^1H NMR (300 MHz, $CDCl_3$): δ_H 9.42 (s, 1H), 7.52 (d, *J* 7.4 Hz, 2H), 7.28 (t, *J* 7.4 Hz, 1H), 7.24–7.07 (m, 7H), 4.39 (t, *J* 7.2 Hz, 2H), 2.96 (t, *J* 7.6 Hz, 2H), 2.52 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 191.8, 180.3, 150.6, 141.4, 138.8, 132.1, 131.5, 130.5, 128.9, 127.7, 127.6, 127.5, 125.4, 116.4, 48.5, 26.2, 25.6. HRMS-EI *m/z* $[M]^+$ calcd for $C_{21}H_{17}NO_2^+$ 315.1254, found 315.1278. X-ray crystal structure details of compound **32** (CCDC-1995288): crystallized from hexane–CH_2Cl_2, formula: $C_{21}H_{17}NO_2$, *M* 315.36, color of crystal: brown, blocks, crystal size 0.38 × 0.25 × 0.16 mm^3, *a* 8.4426(1) Å, *b* 15.6454(2) Å, *c* 12.3360(2) Å, β 97.055(1)°, *V* 1617.10(4) Å^3, ρ_{calc} 1.295 g/m^3, μ 0.083 mm^{-1}, *F*(000) 664, *Z* = 4, monoclinic, space group $P2_1/c$, *T* 173(2) K, 15232 reflections collected, 3997 independent reflections, θ_{max} 28.270°, 217 refined parameters, maximum residual electron density 0.281 and −0.223 e.Å^{-3}. R_1 0.0274, wR_2 0.1038.

(5-Bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone (**33a**). NBS (979 mg, 5.50 mmol) was added to a solution of phenyl(6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)methanone (**17a**) (1.377 g, 4.79 mmol) in dry THF (25 mL), and the mixture was stirred at room temperature under Ar for 20 min. The solvent was evaporated and the residue was extracted with EtOAc (50 mL). The extract was washed with H_2O (2 × 50 mL) and brine (25 mL), dried over Na_2SO_4, filtered and evaporated to give an orange gum. Flash chromatography (10% EtOAc/hexane to 20% EtOAc/hexane) afforded (5-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone (**33a**) (952 mg, 2.60 mmol, 54%) as a cream solid which was used immediately into the next set of reactions as it decomposed rapidly upon isolation. The low yield may be attributed to decomposition of the product during the course of chromatography, and clean NMR spectra could not be obtained. ^1H NMR (300 MHz, $CDCl_3$): discernible signals δ_H 7.58 (d, *J* 7.2 Hz, 2H), 7.31 (t, *J* 7.3 Hz, 1H), 7.27–7.06 (m, 7H), 4.01 (t, *J* 7.2 Hz, 2H), 2.93 (t, *J* 7.4 Hz, 2H), 2.48 (quintet, *J* 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$):

δ_C 191.5, 144.6, 139.6, 134.1, 131.4, 130.0, 129.2, 127.8, 126.6, 116.4, 113.0, 97.3, 47.3, 27.4, 26.0. HRMS-EI *m/z* [M]$^+$ calcd for $C_{20}H_{16}{}^{79}BrNO^+$ 365.0410, found 365.0410.

[5-Bromo-6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**33b**). NBS (269 mg, 1.51 mmol) was added to a solution of [6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**19**) (499 mg, 1.44 mmol) in dry THF (25 mL), and the mixture was stirred at room temperature under Ar for 1 h. The solvent was evaporated and the residue was extracted with EtOAc (25 mL). The extract was washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and evaporated to give a red gum. Flash chromatography (30% EtOAc/hexane) afforded [5-bromo-6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**33b**) (483 mg, 1.13 mmol, 78%) as a yellow foam that turned black within several hours of isolation. The product was used immediately into the next set of reactions as it tended to decompose rapidly upon isolation; R_f (40% EtOAc/hexane) 0.41. Clean NMR spectra could not be obtained, but discernible signals are as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.57 (d, *J* 7.3 Hz, 2H), 7.32 (t, *J* 7.3 Hz, 1H), 7.24–7.13 (m, 2H), 6.83 (dd, *J* 8.2, 1.6 Hz, 1H), 6.75–6.65 (m, 2H), 4.03 (t, *J* 7.2 Hz, 2H), 3.82 (s, 3H), 3.71 (s, 3H), 2.99 (t, *J* 7.5 Hz, 2H), 2.51 (quintet, *J* 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 191.65, 148.2, 147.7, 144.7, 139.6, 131.4, 129.1, 128.9, 127.8, 126.8, 122.4, 113.6, 110.7, 97.0, 55.9, 55.8, 47.3, 27.4, 25.9. LRMS: *m/z* (%): 426 (24), 410 (5), 386 (10), 372 (9), 346 (100), 330 (27), 105 (83), 77 (19). A molecular ion could not be obtained by HRMS as the sample decomposed too rapidly.

(5,6-Diphenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone (**34a**). (5-Bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone (**33a**) (350 mg, 0.96 mmol) was added to a flask containing phenylboronic acid (183 mg, 1.50 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol) and Na_2CO_3 (1.06 g, 10.0 mmol). The flask was evacuated and back-filled with Ar several times to remove O_2. A thoroughly degassed mixture of H_2O (5 mL), EtOH (5 mL) and DME (5 mL) was added to the solids under a positive pressure of Ar. The heterogeneous mixture was stirred at room temperature for 10 min, then heated at reflux for 18 h. After cooling to room temperature, H_2O (25 mL) was added to the black reaction mixture, followed by CH_2Cl_2 (50 mL), and stirring was continued for 5 min. The organic phase was separated and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to give a brown oil. Flash chromatography (10% EtOAc/hexane) afforded (5,6-diphenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone (**34a**) (260 mg, 0.72 mmol, 75%) as a pale-yellow fluffy solid, mp 105–108 °C (sweating noted at 102 °C); R_f (10% EtOAc/hexane) 0.20. IR (ATR, ν_{max}, cm^{-1}): 3057 (w), 2964 (w), 1631 (s), 1597 (m), 1470 (m), 1369 (m), 1278 (m), 1050 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.61 (d, *J* 7.1 Hz, 2H), 7.38–7.10 (m, 8H), 7.02 (br s, 5H), 4.02 (t, *J* 6.7 Hz, 2H), 2.94 (t, *J* 7.0 Hz, 2H), 2.48 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 92.7, 144.6, 140.1, 135.3, 132.0, 131.1, 130.8, 129.6, 129.2, 128.4, 127.7, 127.6, 127.1, 125.8, 115.8, 46.9, 26.7, 26.5. HRMS-EI *m/z* [M]$^+$ calcd for $C_{26}H_{21}NO^+$ 363.1618, found 363.1617.

[5-(3,4-Dimethoxyphenyl)-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**34b**). The above procedure was repeated with (5-bromo-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)(phenyl)methanone (**33a**) (425 mg, 1.16 mmol), 3,4-dimethoxyphenylboronic acid (328 mg, 1.80 mmol), $Pd(PPh_3)_4$ (139 mg, 0.12 mmol), Na_2CO_3 (1.27 g, 12.0 mmol), H_2O (10 mL), EtOH (10 mL) and DME (10 mL). The heterogeneous mixture was stirred at room temperature for 10 min, then heated at reflux for 1 h. Work-up as described above yielded brown oil, which was purified by flash chromatography (10% EtOAc/hexane) to give [5-(3,4-dimethoxyphenyl)-6-phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**34b**) (427 mg, 1.01 mmol, 87%) as a solid yellow foam, mp 59–60 °C; R_f (20% EtOAc/hexane) 0.12. IR (ATR, ν_{max}, cm^{-1}): 3054 (w), 2934 (w), 1633 (s), 1597 (m), 1443 (s), 1204 (s), 1038 (s), 956 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.62 (d, *J* 7.1 Hz, 2H), 7.40–7.25 (m, 1H), 7.25–7.15 (m, 2H), 7.15–6.94 (m, 5H), 6.82 (br s, 2H), 6.55 (s, 1H), 4.04 (t, *J* 6.5 Hz, 2H), 3.85 (s, 3H), 3.51 (s, 3H), 2.92 (t, *J* 6.9 Hz, 2H), 2.48 (quintet, *J* 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 192.5, 148.4, 148.0, 144.3, 140.3, 135.6, 131.0, 130.8, 129.0, 127.7, 127.6, 126.9, 126.7, 125.7, 124.5, 121.2, 115.6, 113.2, 110.9, 55.8, 55.5, 46.9, 26.7, 26.5. HRMS-EI *m/z* [M]$^+$ calcd for $C_{28}H_{25}NO_3^+$ 423.1829, found 423.1828.

[5,6-Bis(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**34c**). The above procedure was repeated with [5-bromo-6-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**33c**) (200 mg, 0.47 mmol), 3,4-dimethoxyphenylboronic acid (130 mg, 0.71 mmol), $Pd(PPh_3)_4$ (55 mg, 0.05 mmol), Na_2CO_3 (498 mg, 4.70 mmol), H_2O (10 mL), EtOH (10 mL) and DME (10 mL). The heterogeneous mixture was stirred at room temperature for 10 min, then heated at reflux for 1 h. Work-up as described above yielded a brown oil, which was purified by flash chromatography with 10% EtOAc/hexane to give [5,6-bis(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolizin-7-yl](phenyl)methanone (**34b**) (181 mg, 0.37 mmol, 80%) as a thick yellow gum, R_f (40% EtOAc/hexane) 0.24. IR (ATR, ν_{max}, cm^{-1}): 2935 (w), 2834 (w), 1699 (w), 1516 (s), 1496 (m), 1237 (s), 1137 (s), 1022 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.62 (d, *J* 7.5 Hz, 2H), 7.32 (t, *J* 7.4 Hz, 1H), 7.20 (t, *J* 7.5 Hz, 2H), 6.82 (s, 2H), 6.66–6.53 (m, 4H), 4.04 (t, *J* 7.0 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.59 (s, 3H), 3.57 (s, 3H), 2.95 (t, *J* 7.3 Hz, 2H), 2.49 (quintet, *J* 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 192.6, 148.4, 148.0, 147.9, 147.1, 144.4, 140.3, 131.0, 128.9, 128.2, 127.6, 126.7, 126.2, 124.6, 123.1, 121.5, 115.4, 114.4, 113.0, 110.9, 110.7, 55.80, 55.77, 55.62, 55.57, 46.8, 26.54, 26.45. HRMS-EI *m/z* [M]$^+$ calcd for $C_{30}H_{29}NO_5^+$ 483.2040, found 483.2009.

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Supplementary Material

Supplementary data associated with this article (^{1}H and ^{13}C{^{1}H} NMR spectra) can be found in the online version.

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