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# Chromenone-Fused Pyrrolizines and Pyrrolizine Analogues of Lamellarins: Expanding the Lamellarin Family

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Several *N*-ethoxycarbonylmethyl enaminones, prepared by Eschenmoser sulfide contraction between *N*-(ethoxycarbonylmethyl)pyrrolidine-2-thione and various *ortho*-oxygenated phenacyl halides, underwent cyclisation to give ethyl 6-aryl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylates upon microwave heating with silica gel in xylene. With enaminones made from *ortho*-hydroxyphenacyl halides, not only did dihydropyrrolizine formation take place, but spontaneous lactonisation also occurred to give 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-ones. Bromination and Suzuki-Miyaura arylation of these chromenopyrrolizines at the free C–H site on the pyrrole ring afforded four analogues of the lamellarin alkaloids in which a pyrrolidine ring replaces the isoquinoline system in the fused polycyclic core. The product 11-(3,4-dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one, in particular, is a congener of the well-known lamellarin G trimethyl ether. Preliminary results pertaining to an extension to chromenone-fused indolizines are also reported.

## Introduction

The chemistry and biological activities of the lamellarins, a notable group of marine metabolites found in a variety of sponges, molluscs and ascidians, have been extensively documented in several recent reviews.[1] More than fifty of these natural products possess a pentacyclic core containing a fully-substituted central pyrrole ring fused to an isoquinoline component in a [2,1-*a*] fashion, and to a chromen-2-one (= coumarin) across its C2-C3 bond, as shown in **1** (Figure 1; conventional lamellarin numbering shown[1c]). A pendent aryl substituent is invariably also present at C-1. In view of the pronounced anticancer activity of representative alkaloids such as lamellarin D (**2**), lamellarin N (**3**) and lamellarin X (**4**), and synthetic analogues such as dehydrolamellarin J (**5**),[2] much recent effort has gone into the synthesis of lamellarins and their analogues,[3] and new methodology has often been trialled in formal or total syntheses of the simple derivative lamellarin G trimethyl ether (**6**).[4] Attention has also been paid to the synthesis of unnatural lamellarin variants in the hopes of finding compounds with more potent pharmacological activity. In general, these efforts have focused on ringing the changes on substituents attached to the various aromatic rings or, occasionally, by replacing the pendent aryl group with other substituents. Some isomers of the pentacyclic scaffold with different points of fusion between the pyrrole and chromen-2-one units[5] or with a chromen-4-one unit[6] – variously termed isolamellarins – have also been reported. However, relatives of the lamellarins in which rings A, B, D or E in the pentacyclic core have been replaced by other ring systems are rather rare. Most frequently encountered are ring B alternatives, especially with a lactam replacing the lactone (azalamellarins),[7] or with contracted rings such as cyclopentanone[8] (i.e. removal of the ring

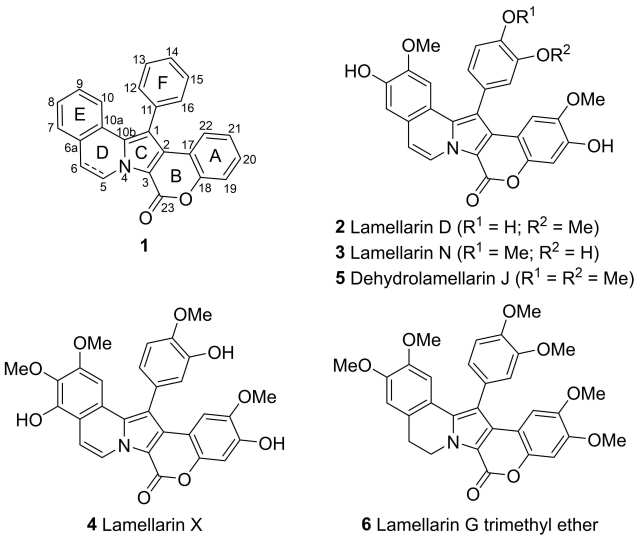


**Figure 1.** Conventional numbering of the lamellarin skeleton, and structures of representative naturally occurring and synthetic lamellarins.

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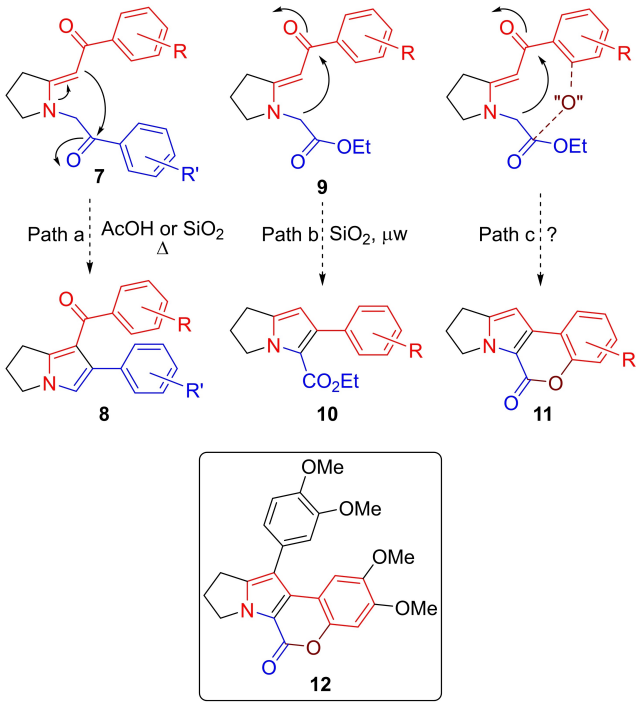
oxygen) or furan[4c] (i.e., removal of the carbonyl group). The only ring D variant reported so far appears to be a compound in which the entire isoquinoline DE ring system has been replaced by a benzazepinone component.[9] An analogue in which ring E has been deleted entirely has been reported recently.[10] Several recent reviews that deal with the synthesis of chromenones fused to various heterocycles, and including coverage of lamellarins and isolamellarins, are also of interest.[11]

We have recently reported short, high-yielding syntheses of lamellarin G trimethyl ether (**6**) as well as several other naturally occurring lamellarins.[12,13] These routes showcased enaminones as pivotal synthetic intermediates, thereby providing further illustrations of our long-standing series of investigations into the use of enaminones for the synthesis of alkaloids and other nitrogen heterocycles.[14] However, in the course of our continuing methodological studies on the chemistry of enaminones, we recently reported two complementary transformations of *N*-acylmethyl enaminones, prepared by Eschenmoser sulfide contraction[15,16] from relevant pyrrolidine-2-thiones and α-halocarbonyl compounds, into 2,3-dihydro-1*H*-pyrrolizines. In the first of these, *N*-phenacyl systems **7** cyclised spontaneously to products **8** on exposure to acetic acid or silica gel, the enaminone acting as a nucleophile towards the carbonyl group of the *N*-phenacyl system (Scheme 1, path a).[17] However, when *N*-ethoxycarbonylmethyl enaminones **9** were subjected to microwave heating in the presence of silica gel, the methylene substituent adjacent to the ester cyclised onto the carbonyl of the enaminone, which behaved as an electrophile to yield dihydropyrrolizines **10**[18] (Scheme 1, path b). This alternative mode of reactivity suggested the intriguing possibility of further cyclisation between the ester and the adjacent aryl substituent, with participation of a suitable oxygen substituent either on the aryl ring or from the ester, to create a coumarin moiety, as in **11** (Scheme 1, path c). If such a cyclisation could be promoted, we believed that we could create an entirely new family of lamellarin look-alikes in which the isoquinoline ring system DE could be replaced by a pyrrolidine ring to give dihydropyrrolizine versions of the natural products. Our findings, culminating in a synthesis of **12**, the pyrrolizine counterpart of lamellarin G trimethyl ether (**6**), and several analogues, are detailed below.

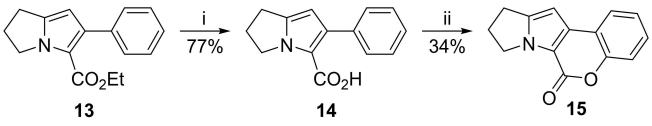



**Scheme 1.** Previous and proposed routes to 2,3-dihydro-1*H*-pyrrolizines from enaminones. Path a shows the enaminone acting as a nucleophile.[17] Path b shows the enaminone acting as an electrophile.[18] Path c is the proposed route in which the enaminone acts as an electrophile with concomitant formation of a fused chromen-2-one system.

## Results and Discussion

Encouraged by previous syntheses of lamellarins and related alkaloids in which the coumarin unit was introduced by lead(IV) acetate-promoted lactone formation between a carboxylic acid and an aromatic ring bearing a hydrogen atom on the site at which the new C–O bond is formed,[3d,f,19] we investigated a similar transformation with our previously prepared[18] pyrrolizine ester **13**. After hydrolysis of the ester with potassium hydroxide in methanol, the resulting acid **14** was treated with lead(IV) acetate in ethyl acetate at room temperature. The desired 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one **15**, a known compound,[20] was formed, but in a disappointing yield of only 34% (Scheme 2). Other workers have also reported unsatisfactory results when attempting similar lead(IV)-mediated lactonisations en route to lamellarins.[5d,21] An alternative approach with enaminones containing a pre-installed phenolic substituent on the aromatic ring was therefore indicated.

In order to prepare the enaminones **16** required for pyrrolizine-lactone formation, the pyrrolidine-2-thione **17** and *o*-oxygenated phenacyl halides **18** were necessary precursors for the Eschenmoser sulfide contraction. We have previously reported the synthesis of **17**,[18] while the requisite halides **18** (X = Br) were readily prepared by bromination of the corresponding acetophenones **19** (Scheme 3). The simple *o*-hydroxy acetophenone **19a**, our model for subsequent investigations, is commercially available, while we have previously reported the synthesis and characterisation of the 3,4-dimethoxy analogue **19b**,[22] which contains substituents more typical of lamellarins. Bromination of **19a** with copper(II) bromide in chloroform-ethyl acetate by a published method[23] gave the desired bromide **20a** in greater than 90% yield, while application of the same method to **19b** afforded **20b** in 84% yield after recrystallisation. On occasion the α,α-dibromo product **21** could be isolated from the mother liquors. Finally, fearing the interference of a




**Scheme 2.** Reagents and conditions: (i) KOH, MeOH, 30–100 °C; (ii) $Pb(OAc)_4$, EtOAc, rt.

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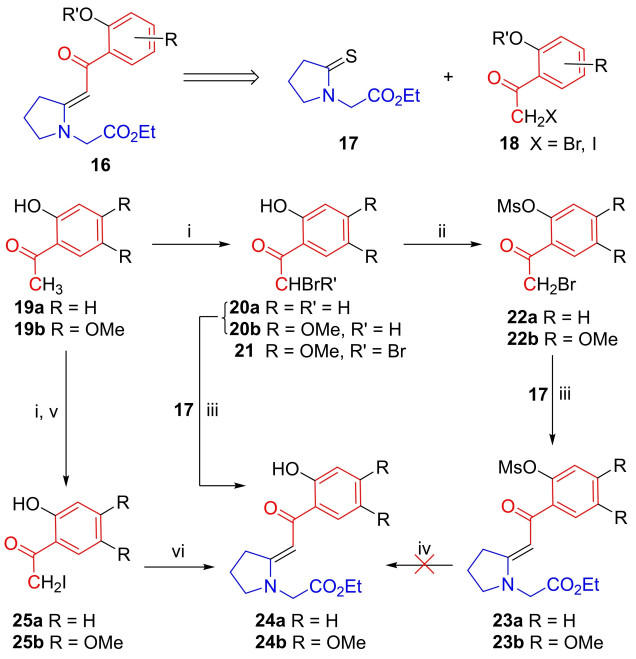



**Scheme 3.** Reagents, conditions and yields: (i) $CuBr_2$, EtOAc-$CHCl_3$, reflux (**20a**, >90%; **20b**, 84%); (ii) $MeSO_2Cl$, $Et_3N$, THF, −15 °C to rt (**22a**, 92%; **22b**, 96%); (iii) MeCN, rt, then $PPh_3$, $Et_3N$, MeCN, rt (**23a**, 86%; **23b**, 62%; **24a**, 89%); (iv) aq. KOH, reflux; (v) NaI, $Me_2C{=}O$, rt (**25a**, 98%; **25b**, 96%); (vi) MeCN, rt, then $PPh_3$, $Et_3N$, MeCN, rt (**24a**, 96%; **24b**, 89%).

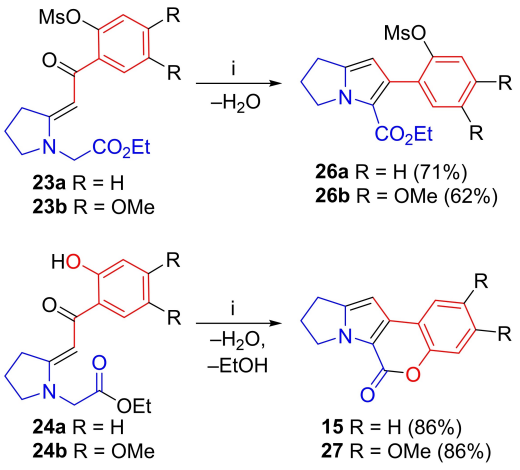
free phenol during subsequent transformations, we chose to protect the OH group of bromides **20** as methanesulfonates by following the example of Ruchirawat and Mutarapat, who had reported a similar protection and ready deprotection strategy in their own approach to lamellarin alkaloids.[24] The protection was performed with methanesulfonyl chloride and triethylamine in tetrahydrofuran, and the mesylated phenacyl bromides **22a** and **22b**, reported but not characterised by Ruchirawat, were obtained in yields of 92% and 96%, respectively.

Salt formation between the thiolactam **17** and *o*-methanesulfonyloxy phenacyl bromides **22** was performed in acetonitrile at room temperature. When thin-layer chromatography indicated complete consumption of the thiolactam, sulfide contraction was induced by the addition of triphenylphosphine and triethylamine to give enaminones **23a** and **23b** in yields of 86% and 62%, respectively. However, all attempts to hydrolyse the mesylated compounds to the free phenols **24** with aqueous potassium hydroxide failed, apparently because of the sensitivity of the enaminone system to the basic conditions as well as interference from the ester.

Fortunately, protection of the free phenol turned out to be unnecessary. The model phenacyl bromide **20a** successfully *S*-alkylated the thiolactam **17** in acetonitrile at room temperature, after which sulfide contraction with triethylamine and triphenylphosphine gave enaminone **24a** in 89% yield. However, salt formation with the methoxy-substituted phenacyl bromide **20b** was inefficient, necessitating its prior conversion into the corresponding iodide **25b**. This was achieved in 96% yield by Finkelstein reaction of **20b** with sodium iodide in acetone. Thereafter, reaction with thiolactam **17** followed by sulfide contraction afforded the desired enaminone **24b** in 89% yield. For comparison, reaction of thiolactam **17** with *o*-hydroxyphenacyl iodide **25a**, also prepared by Finkelstein halide exchange, afforded enaminone **24a** in 96% yield. All four enaminones **23a,b** and **24a,b** were obtained as single geometric isomers, the (*E*)-configurations of which were inferred by comparison with the numerous related phenacyl-derived enaminones that we have previously described.[17,18] Further evidence for the (*E*)-configuration was provided by NOESY NMR spectroscopy, which showed interactions between the vinyl hydrogens (δ 5.4–5.7 ppm) and the methylene unit adjacent to the ester (δ *ca* 4.1). In the case of compounds **24a,b**, the highly deshielded phenolic hydrogens (δ 14.02 and 14.27 ppm, respectively) strongly suggested intramolecular hydrogen bonding to the ketone. Finally, both the geometry of the double bond and the intramolecular hydrogen bond were apparent in an X-ray crystal structure of product **24b** (Figure 2a; CCDC 2311384).

With the enaminones in hand, acid-induced cyclisation to form 2,3-dihydro-1*H*-pyrrolizines was attempted. Microwave heating of the mesylates **23a** and **23b** with silica gel in xylene according to our previously described protocol[18] indeed resulted in formation of products **26a** and **26b**, which were isolated in yields of 71% and 62%, respectively (Scheme 4). The structure of **26b** was confirmed by single-crystal X-ray diffraction (Figure 2b; CCDC 2311385), which proves the formation of the dihydropyrrolizine system and thus supports the participation of the enaminone as an electrophile. With the two phenolic enaminones **24a** and **24b**, however, not only was the dihydropyrrolizine nucleus formed under the same conditions, but spontaneous lactonisation led to the formation of the 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-ones **15** and **27**, both in 86% yield. Results were far poorer when conventional heating of the enaminone/silica gel combination in boiling xylene was attempted: yields of **26a**, **26b**, **15** and **27** were, at best, 53%, 36.5%, 63% and 23%, respectively.

The chromenopyrrolizinones **15** and **27** contain the fused tetracyclic core of our desired pyrrolizine-lamellarin analogues,




**Scheme 4.** Reagents and conditions: (i) $SiO_2$, xylene, microwave heating (150 W, 180–200 °C).

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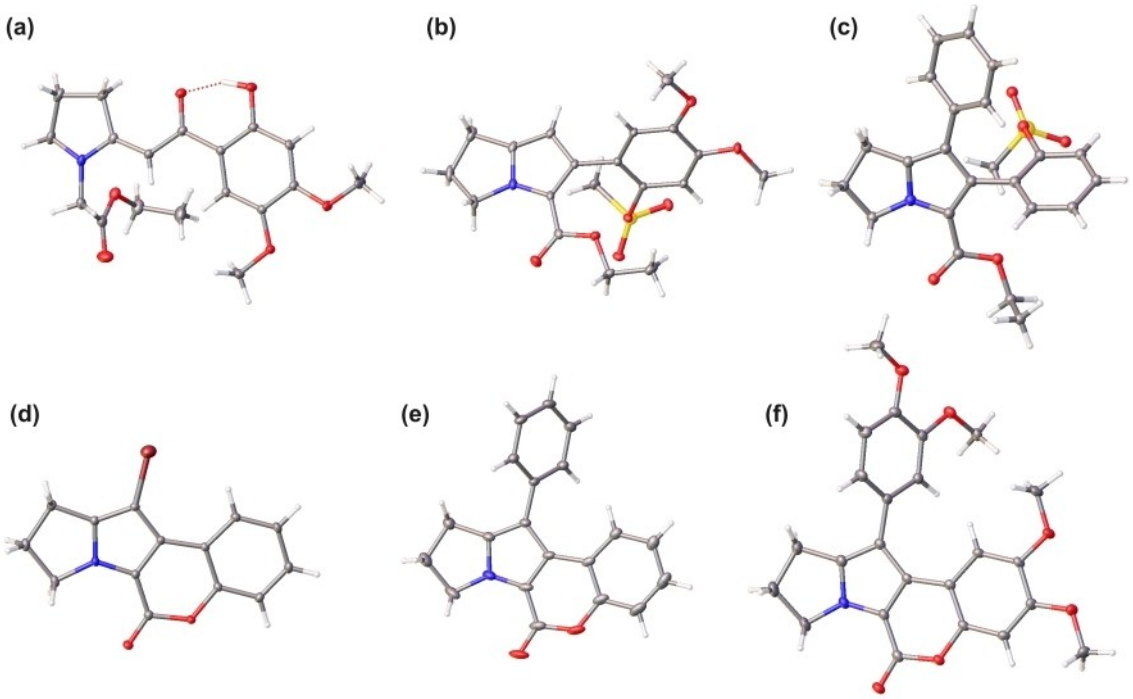
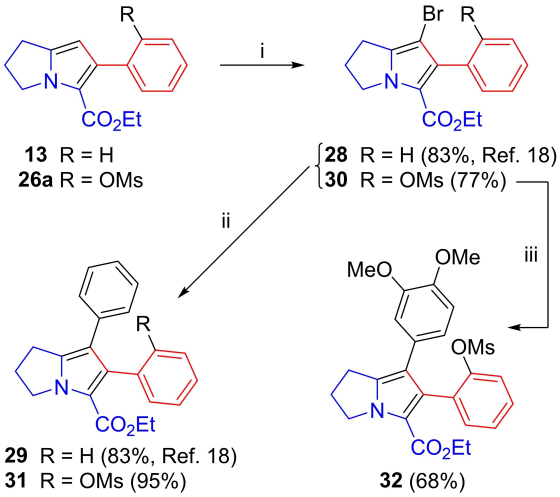



**Figure 2.** ORTEP diagrams of the crystal structures of: (a) ethyl (*E*)-2-{2-[2-(2-hydroxy-4,5-dimethoxyphenyl)-2-oxoethylidene]pyrrolidin-1-yl}acetate (**24b**), showing the intramolecular hydrogen bond; (b) ethyl 6-[4,5-dimethoxy-2-(methylsulfonyloxy)phenyl]-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (**26b**; one of two molecules in the asymmetric unit is shown); (c) ethyl 6-{2-[(methylsulfonyl)oxy]phenyl}-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxylate (**31**); (d) 11-bromo-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (**33**); (e) 11-phenyl-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (**35**); (f) 11-(3,4-dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (**12**; the pyrrolidine ring is disordered, and only the major conformation (85%) is shown). Thermal ellipsoids are at 50% probability.

requiring only the attachment of the pendent aryl ring F to complete the synthesis. A common protocol in the synthesis of the natural products is to brominate the remaining unsubstituted carbon atom on the pyrrole ring, after which the aromatic ring is attached by Suzuki-Miyaura coupling with suitable aryboronic acids.[1c] We had previously proved that this approach is suitable for arylating the dihydropyrrolizine core by brominating the bicyclic precursor **13** with *N*-bromosuccinimide (NBS) in dimethylformamide to give **28** (83%), and then coupling this intermediate with phenylboronic acid to yield the fully substituted pyrrole **29** (83%)[18] (Scheme 5). We adopted this strategy for the introduction of ring F into our proposed lamellarin analogues. We first confirmed this strategy with the mesylate model **26a**, bromination of which was readily performed with *N*-bromosuccinimide in dimethylformamide to give **30** in 77% yield. The subsequent Suzuki-Miyaura coupling was tested both with phenylboronic acid and with 3,4-dimethoxyphenylboronic acid, using tetrakis(triphenylphosphine)palladium(0) as catalyst. Conditions for the coupling proved to be tricky: with phenylboronic acid itself, the best yield (95%) of the desired phenylated product **31** was obtained under reflux conditions with degassed 1,2-dimethoxyethane and aqueous sodium carbonate as base. The structure of this product was confirmed crystallographically (Figure 2c; CCDC 2311386). However, with 3,4-dimethoxyphenylboronic acid, the best results were obtained by




**Scheme 5.** Reagents and conditions: (i) NBS, DMF, 0 °C to rt; (ii) $Pd(PPh_3)_4$ (0.1–0.3 equiv.), $PhB(OH)_2$, aq. $Na_2CO_3$ (2 M), $MeOCH_2CH_2OMe$, EtOH, rt to reflux; (iii) $Pd(PPh_3)_4$ (0.05 equiv.), 3,4-$(MeO)_2C_6H_3B(OH)_2$, $Na_2CO_3$, DMF-$H_2O$ (1:1), microwave irradiation (150 W, 150 °C).

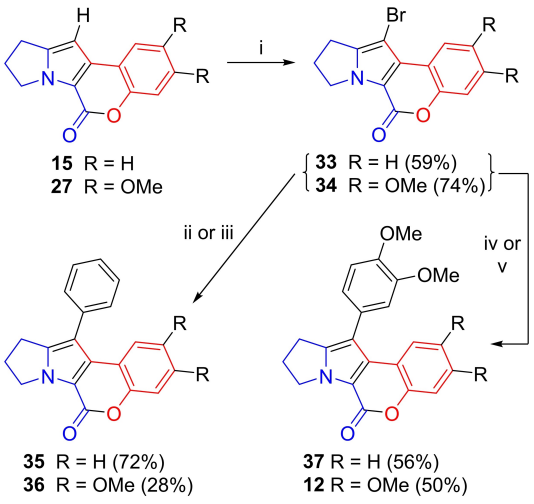
microwave irradiation in a mixture of water and dimethylformamide, giving the coupled product **32** in 68% yield.

The series of model investigations having been completed successfully, the concluding set of experiments aimed at the synthesis of chromenopyrrolizinone analogues of the lamellarins was undertaken. Bromination of the relevant tetracyclic intermediates **15** and **27** with *N*-bromosuccinimide in dimeth-

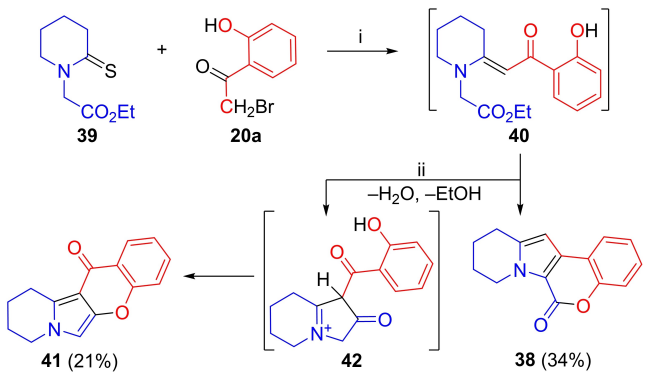
ylformamide afforded, after careful recrystallisation, the rather sensitive products **33** and **34** in isolated yields of 59% and 74% yields, respectively (Scheme 6). The structure of **33** was confirmed by single-crystal X-ray diffraction of a sample obtained by recrystallisation from dichloromethane-hexane (Figure 2d; CCDC 2311387). The subsequent Suzuki-Miyaura coupling of both bromides was then tested with phenylboronic acid and tetrakis (triphenylphosphine)palladium(0) as catalyst. Heating **33** with these reactants in a mixture of 1,2-dimethoxyethane and ethanol (1:1) with aqueous sodium carbonate as base produced the arylated product **35** in 72% yield after purification by column chromatography and recrystallisation, thereby giving us our first example of a pyrrolizine-containing lamellarin analogue. The structure of **35** was supported by the usual range of spectroscopic techniques, as well as by X-ray crystallography (Figure 2e; CCDC 2311388). A similar coupling of the bromopyrrolizine **34** with phenylboronic acid and cesium carbonate as base was less successful, eventually giving **36** in an unoptimised yield of 28%.

Next, Suzuki-Miyaura couplings of **33** and **34** with 3,4-dimethoxyphenylboronic acid was carried out to produce the final set of lamellarin analogues. These couplings proved to be problematic, and required much fine-tuning of conditions to give acceptable yields. The DMF-water solvent system with added solid sodium hydrogen carbonate under microwave conditions worked best with brominated intermediate **33**, and gave the coupled product **37** in 56% yield. Finally, the coupling of methoxylated chromenopyrrolizinone **34** was accomplished under conditions described by Qiu *et al.*,[25] which entailed the use of cesium fluoride and silver(I) oxide in 1,2-dimethoxyethane at 80 °C. The product **12** was thereby obtained in 50% yield. The structure of compound **12** – the desired pyrrolizine analogue of lamellarin G trimethyl ether (**6**) – was substantiated by single-crystal X-ray diffraction (Figure 2f; CCDC 311383).

As a further amplification of the lamellarin family, we undertook a preliminary investigation of a possible extension to the 8,9,10,11-tetrahydro-6*H*-chromeno[4,3-*b*]indolizin-6-one system **38**. This required adapting the strategy illustrated in Schemes 3 and 4 by starting with **39**,[18] the piperidine analogue of thiolactam **17**. However, *S*-alkylation of **39** with *o*-hydroxyphenacyl bromide (**20a**) followed by sulfide contraction proved to be thoroughly unsatisfactory, since the desired enaminone **40** was always contaminated with inseparable by-products from the thiophile, irrespective of whether triphenylphosphine or triethyl phosphite was employed. Such contamination with phosphorus-containing by-products is a well-documented problem in Eschenmoser sulfide contractions.[16] Nevertheless, a small sample of relatively pure **40** was heated with silica gel and xylene at 180 °C in a microwave reactor at 150 W in an attempt to force indolizine formation and concomitant lactonisation. The surprising result was that not only could product **38**, resulting from the expected reactivity of the enaminone as an electrophile, be isolated in approximately 34% yield, but a second isomer was also formed in about 21% yield (Scheme 7). From spectroscopic analysis the chromen-4-one structure **41** was inferred. Whereas the lactone structure **38** displayed a $^{13}$C NMR spectroscopic signal for the carbonyl group at δ 155.2, the carbonyl signal for the new compound **41** was located at δ 175.6, a typical value for a chromen-4-one. This chemical shift is also quite similar to values reported for various structurally similar chromeno[2,3-*c*]pyrrol-9(2*H*)-ones (δ 172–176).[26] In this case, the enaminone apparently acts as a nucleophile via its enamine carbon atom, which reacts with the carbonyl of the ester to give an intermediate such as **42**, in this way forming the C1-C2 bond of the indolizine nucleus. The phenol subsequently reacts at the newly generated C2 carbonyl group with the expulsion of water, thus completing the formation of the 4-chromenone ring. In relation to our previous work with phenacyl-derived enaminones,[17,18] this is the first time we have observed dual reactivity of such substrates, and further studies with piperidines and larger saturated nitrogen heterocycles are warranted.




**Scheme 6.** Reagents and conditions: (i) NBS, DMF, 0 °C to rt; (ii) **33**, $Pd(PPh_3)_4$ (0.26 equiv.), $PhB(OH)_2$, aq. $Na_2CO_3$ (2 M), $MeOCH_2CH_2OMe$, EtOH, rt to reflux; (iii) **34**, $Pd(PPh_3)_4$ (0.09 equiv.), $PhB(OH)_2$, $Cs_2CO_3$, $MeOCH_2CH_2OMe$, microwave irradiation (150 W, 150 °C); (iv) **33**, $Pd(PPh_3)_4$ (0.06 equiv.), 3,4-$(MeO)_2C_6H_3B(OH)_2$, $Na_2CO_3$, DMF-$H_2O$ (1:1), microwave irradiation (150 W, 150 °C); (v) **34**, $Pd(PPh_3)_4$ (0.2 equiv.), 3,4-$(MeO)_2C_6H_3B(OH)_2$, CsF, $Ag_2O$, $MeOCH_2CH_2OMe$, 80 °C.




**Scheme 7.** Reagents and conditions: (i) NaI, MeCN, rt, then $P(OEt)_3$, $Et_3N$, MeCN, 0 °C to rt; (ii) $SiO_2$, xylene, microwave irradiation (150 W, 180 °C).

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## Conclusions

The tandem cyclocondensation-lactonisation of enaminones derived from *ortho*-hydroxy phenacyl halides and *N*-(ethoxycarbonylmethyl)pyrrolidine-2-thione upon microwave heating with silica gel has proved to be an efficient, rapid and relatively green procedure for making 9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-ones. This heterocyclic system is effectively a tetracyclic variant of the pentacyclic core of the lamellarin alkaloids in which a pyrrolidine ring replaces an isoquinoline unit while retaining the chromeno[3,4-*b*]pyrrol-4(3*H*)-one moiety of the natural products. Subsequent bromination of the free CH site on the central pyrrole ring followed by Suzuki-Miyaura arylation allows introduction of the pendent aromatic ring that is also a characteristic feature of most lamellarins. Four pyrrolizine-containing analogues of the alkaloids were synthesised, including compound **12**, a congener of lamellarin G trimethyl ether (**6**), which is the benchmark system for testing new methodology for lamellarin synthesis. Preliminary results on tandem cyclocondensation-chromenone formation with a piperidine-containing enaminone homologue showed an intriguing duality of reaction in which both the electrophilicity and the nucleophilicity of the enaminone were observed. This extension, and further extensions to enaminones containing other heterocyclic units, merit further investigation.

## Experimental Section

General information, experimental procedures for the synthesis of all compounds, characterisation data, crystallographic details, and NMR spectra are provided in the Supporting Information.

**General procedure for the synthesis of ethyl (*E*)-2-[2-(2-aryl-2-oxoethylidene)pyrrolidin-1-yl]acetates**: To solution of ethyl 2-(2-thioxo-1-pyrrolidinyl)acetate (**17**) (1.0 mmol) in anhydrous MeCN (*ca* 2 mL mmol$^{-1}$) was added the appropriate phenacyl halide (1.2 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature until TLC indicated consumption of the thiolactam (15–30 min). A solution of triphenylphosphine (1.2 mmol, 1.2 equiv.) and triethylamine (1.2–2.0 mmol, 1.2–2.0 equiv.) in MeCN (5 mL) was added dropwise over 10–15 min, and the resulting mixture was stirred at room temperature for the stipulated time (see Supporting Information). The solvent was removed and the residue was extracted into EtOAc. The extract was washed with water and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product thus obtained was purified by flash column chromatography with EtOAc-hexane mixtures to afford the corresponding ethyl (*E*)-2-[2-(2-aryl-2-oxoethylidene)pyrrolidin-1-yl]acetates **23 a**, **23 b**, **24 a** and **24 b**.

**General procedure for acid-induced pyrrolizine formation**: Flash silica gel (5-10 times mass of starting material) was added to a solution of the enaminone in xylene (*ca* 10 mL mmol$^{-1}$) in a capped microwave tube. The mixture was irradiated under microwave conditions (150 W, 180–200 °C, *ca* 15 min) while maintaining moderate stirring. The reaction mixture was filtered through a plug of Celite®, which was then rinsed with acetone until the filtrate became colourless. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography with EtOAc-hexane mixtures. Compounds **15**, **26 a**, **26 b** and **27** were obtained by this procedure.

**General procedure for the bromination of 2,3-dihydro-1*H*-pyrrolizines**: A solution of NBS (1.1 equiv.) in DMF (3–6 mL mmol$^{-1}$) was added dropwise to an ice-cold solution of the 2,3-dihydro-1*H*-pyrrolizines in DMF (3-6 mL mmol$^{-1}$) under an atmosphere of Ar. The reaction mixture was stirred at 0 °C for 1 h, then maintained at room temperature for a further 20 h. The mixture was then quenched with water and extracted with $Et_2O$. The extract was washed with water and brine, dried over $Na_2SO_4$ and evaporated *in vacuo*, and the crude products were purified by recrystallisation. Compounds **30**, **33** and **34** were obtained by this procedure.

### General procedures for the Suzuki-Miyaura arylation of 7-bromo-2,3-dihydro-1H-pyrrolizines

*General method 1:* Tetrakis(triphenylphosphine)palladium(0) (0.1–0.3 equiv.) was added to a two-necked round bottomed flask fitted with a dropping funnel and a reflux condenser, and the system was degassed five times with Ar. The bromo compound (1 equiv.), phenylboronic acid (1.5 equiv.) and 1,2-dimethoxyethane (*ca* 7 mL mmol$^{-1}$ of bromo precursor) were introduced into the dropping funnel, and the system was degassed for a further 10 min. EtOH (5 mL mmol$^{-1}$) was also added to the dropping funnel if necessary to ensure complete dissolution of the contents. The resulting solution was then dropped into the main reaction vessel over 15 min, after which an aqueous solution of degassed $Na_2CO_3$ (2 M; 2.5 mL mmol$^{-1}$) was added from the dropping funnel, and the final mixture was heated at reflux for 20 h under an atmosphere of Ar gas. On cooling, water (25–30 mL mmol$^{-1}$) was added, and the mixture was extracted with several portions of EtOAc. The collected organic fractions were washed with brine, dried over $Na_2SO_4$, filtered and evaporated *in vacuo* to give the crude products **31** and **35**, purification of which was carried out by column chromatography and/or recrystallisation.

*General method 2:* A capped microwave vessel was charged with the bromo compound (1 equiv.), 3,4-dimethoxyphenylboronic acid (1.3 equiv.), $NaHCO_3$ (3.0 equiv.) and $Pd(PPh_3)_4$ (6 mol%.) in a mixture of DMF and water (1 : 1; *ca* 16 mL mmol$^{-1}$). The reaction mixture was then subjected to microwave irradiation (150 W, 150 °C) for 15 min. The cooled reaction mixture was then extracted into $Et_2O$ (*ca* 50 mL mmol$^{-1}$), which was washed with water (20 mL), and the aqueous layer was back-extracted further with $Et_2O$ (3×40 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and evaporated *in vacuo* to give the crude products **32** and **37**, purification of which was carried out by column chromatography and/or recrystallisation.

**11-(3,4-Dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (12)**: Conditions for Suzuki-Miyaura coupling described by Qiu *et al.*[25] were used in this reaction. A mixture of 11-bromo-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (**34**) (73 mg, 0.20 mmol), 3,4-dimethoxyphenylboronic acid (67 mg, 0.37 mmol), CsF (67 mg, 0.44 mmol), $Ag_2O$ (80 mg, 0.35 mmol), $Pd(PPh_3)_4$ (47 mg, 0.041 mmol) and 1,2-dimethoxyethane (4 mL) was heated at 80 °C with stirring for 22 h. On cooling, water (10 mL) was added, and the mixture was extracted into $CH_2Cl_2$ (3×10 mL). The organic extracts were combined and washed with water (10 mL) and brine (10 mL). The organic phase was dried over $Na_2SO_4$, filtered and evaporated *in vacuo*. The residue obtained was purified by flash column chromatography (EtOAc-hexane 3 : 7). Recrystallisation from EtOAc-hexane gave 11-(3,4-dimethoxyphenyl)-2,3-dimethoxy-9,10-dihydrochromeno[4,3-*b*]pyrrolizin-6(8*H*)-one (**12**) as yellow plates (42 mg, 50 %); $R_f$ = 0.21 (EtOAc-hexane 1 : 1); m.p. 223–225 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.09 (s, 1H), 7.05–6.98 (m, 3H), 6.91 (s, 1H), 4.47 (t, $J$ = 7.2 Hz, 2H), 3.95 (s, 3H), 3.90 and 3.89 (2 × s, 6H), 3.57 (s, 3H), 2.96 (t, $J$ = 7.4 Hz, 2H), 2.64 (quintet, $J$ = 7.3 Hz, 2H); $^{13}$C

NMR (75 MHz, $CDCl_3$): $\delta = 155.7$, 149.1, 149.0, 148.5, 147.1, 146.4, 145.6, 130.3, 127.3, 122.4, 113.3, 112.3, 112.1, 111.4, 111.2, 105.0, 101.0, 56.20, 56.16, 56.11, 56.03, 47.5, 27.2, 24.4; IR (ATR): $\tilde{\nu} = 3085$ (w), 2952 (w), 2839 (w), 1703 (s), 1621 (w), 1587 (w), 1547 (m), 1499 (m), 1466 (m), 1440 (m), 1413 (s), 1327 (m), 1254 (s), 1237 (s), 1224 (m), 1196 (m), 1175 (m), 1157 (s), 1141 (s), 1083 (m), 1045 (m), 1021 (s), 1004 (s), 929 (m), 854 (s), 820 (m), 792 (m), 759 (m), 719 (m), 611 (m) $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{24}NO_6^+$: 422.1598 $[M + H]^+$; found 422.1609.

Deposition Number(s) 2311383 (for **12**), 2311384 (for **24b**), 2311385 (for **26b**), 2311386 (for **31**), 2311387 (for **33**) and 2311388 (for **35**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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