Chapter 6

Total synthesis of selected pyrrole containing marine natural products

6.1 Introduction

A rapidly increasing number of biologically active pyrrole alkaloids, isolated recently from marine sources, possess a common 3,4-diaryl-substituted pyrrole nucleus bearing 2-carboxylate functionality. Lamellarin O 1a is a prototypical member of this class of natural products, which was first, isolated from the southern Australian marine sponge Dendrilla cactos by Capon (1994). It has been reported that biological activity could not be determined for natural lamellarin O due to its instability and limited availability. Lamellarin Q 1b was also isolated from the same sponge specimen. Lukianol A, 2 a structurally related compound, was discovered in an unidentified Pacific tunicate by Scheuer (1992) and shown to exhibit cytotoxic activity against a cell line derived from human epidermatoid carcinoma (KB). More recent investigations of related lamellarins have confirmed their cytotoxic activity, revealed equally effective cytotoxic activity against multidrug-resistant (MDR) cell lines, and demonstrated that even at non-cytotoxic concentrations they reverse MDR by inhibiting P-gp-mediated drug efflux.
Recently several structurally related alkaloids have been isolated from widely varying locations and organisms. For example, stomiamide A is a new class of secondary metabolites isolated in 1996 from a Patagonian sponge off the coast of Argentina. Ningalin B, isolated by Fenical (1997) from an ascidian of genus Didemnum collected in western Australia near Nigaloo Reef. Halitulin, a strongly cytotoxic bisquinolinyl pyrrole derivative, was isolated (1999) from the Indo-Pacific sponge *Haliclona tulearensis*. A fundamentally important feature of these compounds is that many of these agents like ningalin B, stomiamide A were found to be capable of reversing MDR at non-cytotoxic concentration resensitising HCT116/VM46 to vinblastine and doxorubicin. Among these new classes of compounds, lamellarin O was found to exhibit micromolar cytotoxicity against wild type and multidrug-resistant tumor cell lines, suggesting it as a new lead for the development of antitumor agents insensitive to MDR.
Another biologically active pyrrole containing marine natural product Rigidin 6, isolated and characterized in 1990 by Kobayshi, et al. from the Okinawan marine tunicate *Eudistoma cf. rigida* was found to inhibit calmodulin activated brain phosphodiesterase.\(^9\)

![Rigidin 6](image)

It is obvious from a close analysis of these structures that the methods we have developed for the synthesis of substituted pyrroles, described in the preceding chapter, can be applied to the realization of their total synthesis. Our synthetic strategy starts with the preparation of \(\beta\)-oxodithioesters from substituted \(\alpha\)-arylacetoephonones using dimethyl trithiocarbonate followed by displacement of
methylthio group with glycine ester. Alkylation of the intermediate thioamide followed by cyclization of the resulting ketene N,S-acetals under Vilsmeier condition affords the pyrrole skeleton which on desulphurization using Raney nickel generates the alkaloid core. This can be converted into the respective natural products by known procedures.

6.2 Total synthesis of lamellarin O and related alkaloids: An overview

Despite the intriguing biological properties and relatively simple structures only a few studies directed towards the total synthesis of these natural products have been reported to date. The main obstacle for the total synthesis is the unavailability of efficient methods for the preparation of 3,4-diarylpyrrole-2-carboxylates, the central molecular framework of these natural products. An overview of the different approaches made by various groups for synthesizing this class of important natural products is presented below.

6.2.1 Furstner synthesis

Furstner and co-workers have reported the first synthesis of lukianol A and lamellarin O in 1995, immediately after their discovery. They have developed a titanium-induced cyclization of readily accessible enaminoketones 10 to substituted pyrrole derivatives 11 and applied that method for the total synthesis of lukianol A (2) and lamellarin O dimethylether 12 (Scheme 1). Even though the method is concise it produces the target molecule only in 12% overall yield, particularly due to the low yielding titanium induced cyclization.
Key: $\text{Ar} = \text{p-MeOC}_6\text{H}_4$ (a) $\text{H}_2\text{O}_2$, $\text{NaOH}$, $\text{EtOH/H}_2\text{O}$, $0^\circ\text{C} - \text{rt}$, 98%; (b) (i) $\text{BF}_3\cdot\text{Et}_2\text{O}$, reflux; (ii) $\text{NH}_2\text{OH}$, $\text{HCl}$, pyridine, $\text{EtOH}$, reflux, 67% (over both steps); (c) $\text{H}_2$ (1 atm), $\text{Pd}$ (5%), charcoal, $\text{THF}$, 94%. (Z):(E) = 1:1; (d) $\text{ClOCCO}_2\text{Me}$, pyridine, $\text{THF}$, 73%. (Z):(E) = 2.5:1; (e) Ti-Graphite ($\text{TiCl}_3$:K = 1:2), $\text{DME}$, reflux, 52%; (f) p-$\text{MeOC}_6\text{H}_4\text{COCH}_2\text{Br}$, K$_2$CO$_3$, acetone, reflux, 91%; (g) (i) KO-Bu, $\text{H}_2\text{O}$, $\text{Et}_2\text{O}$, $0^\circ\text{C} - \text{rt}$; (ii) $\text{Ac}_2\text{O}$, $\text{NaOAc}$, reflux, 59% (over both steps); (h) $\text{BBr}_3$, CH$_2$Cl$_2$, -78 $^\circ\text{C} - \text{rt}$, 99%.

**Scheme 1**

6.2.2 *Banwell's Method*

After Furstner has reported the synthesis of lukianol A and lamellarin O the main task of synthetic chemists for realizing analogous targets has become development of efficient methods for the construction of 2,4-diarylpyrrole-2-carboxylate core similar to the Furstner intermediate 11.

Banwell’s method for the preparation of analogues of 11 involves a three-step sequence starting from N-trisopropylsilyl pyrrole 13a. The pyrrole was then tribrominated with 3 molar equiv. of NBS to afford the pyrrole 13b. This latter
compound when subjected to reaction with PhLi followed by methyl chloroformate affords $^{13c}$. which on Stille cross-coupling with arylstannane gave $^{14}$. This on deprotection afforded lamellarin Q. The pyrrole $^{13c}$ was desylilicated and the resulting pyrrole $^{16}$ on coupling with arylstannane $^{15}$ gave $^{11}$. This on reaction with commercially available 2-bromo-4'-methoxyacetophenone in the presence of base gave the N-substituted pyrrole $^{12}$ which on deprotection affords lamellarin O. Two-fold cross-coupling of pyrrole $^{16}$, with $p$-MeOC$_6$H$_4$-B(OH)$_2$ under standard Suzuki conditions affords $^{17}$, which was previously converted over three steps into lukianol A by Furstner and co-workers. (Scheme 2).$^{12}$

Reagents and conditions: (a) NBS (3 equiv.), THF, -78 °C, 1 h then 20 °C for 4 h; (b) Ph Li (1 equiv.), -78 °C, 0.16 h then ClCO$_2$Me (1.05 equiv.). -70 to 20 °C. 1 h; (c) Pd(PPh$_3$)$_2$Cl$_2$ (10 mol%), 1,4-dioxane, 101 °C, 14 h; (d) Bu$_4$NF (10 mol% excess), THF, 20 °C, 1 h then 0.5 M aq. HCl; (e) p-MeOC$_6$H$_4$COCH$_2$Br (3 equiv.), K$_2$CO$_3$ (5 equiv.), Bu$_4$NCl (20 mol%), THF, 85 °C, 8 h; (f) Pd(PPh$_3$)$_4$ (5 mol%), sat. aq. Na$_2$CO$_3$ (6 equiv.), DMF, 153 °C, 23 h; (g) BBr$_3$, CH$_2$Cl$_2$, 78 °C, 99%.

Scheme 2
This procedure has been extended for the preparation of differently diarylated analogues of naturally occurring pyrrole alkaloids employing sequential Negashi cross-coupling reactions.

6.2.3 Wong's Method

Wong et al. have developed a highly regioselective synthesis of 2-substituted 3,4-diaryl pyrroles using N-protected 3,4-trimethylsilylpyrrole. Initial α-lithiation of the pyrrole and reaction with methyl chloroformate introduces ester functionality at the two position. The aryl groups are then introduced at 3 and 4 positions by Suzuki coupling reactions. They have utilized this reaction sequence in the synthesis of the marine natural product lukianol A 2 through the Furstner intermediate 11 (Scheme 3).

![Scheme 3](image-url)

Reagents and conditions: (a) I₂, CF₃CO₂Ag, THF, rt, 2h, 100%; (b) ArB(OH)₂, Pd(PPh₃)₄, 2M Na₂CO₃, MeOH/PhMe, 90-100 ºC, 2h. (c) I₂, CF₃CO₂Ag, THF, rt, 1h, 78%; (d) p- MeOC₆H₄B(OH)₂, Pd(PPh₃)₄, 2M Na₂CO₃, DMF, 150 ºC, 1h, 95%; (e) Mg, MeOH, rt, 4h, 85%.
6.2.4 **Boger Synthesis**

Boger et al. have recently reported the total synthesis of ningalin A, lamellarin O, lukianol A, and permethyl stormiamide A, enlisting a common strategy applicable to related natural products and synthetic analogues. Their approach employs a heteroaromatic azadiene Diels-Alder reaction to assemble the substituents onto a six-membered 1,2-diazine core 25, which is followed, by a reductive ring contraction.

Reagents and conditions: (a) PdCl₂(PPh₃)₂, Cul, Et₃N 75%; (b) toluene, 110 °C, 85%; (c) Zn, HOAc, 72%; (d) K₂CO₃, DMF, 70 °C, 100%; (e) (i) LiOH, THF.CH₃OH·H₂O (3:2:1), 50 °C, 76%; (ii) TFA, 97%; (f) H₂, Pd/C, 100%; (g) (i) LiOH, THF.CH₃OH·H₂O (3:2:1), 50 °C, 98%, (ii) NaOAc, Ac₂O, 72%, (iii) BBr₃, CH₂Cl₂, 72%.

**Scheme 4**
reaction\textsuperscript{16,17} to provide the corresponding pyrrole 26, a five membered heteroaromatic system (Scheme 4). The same approach has been latter utilized by them for the total synthesis of Ningalin B, a potent MDR reversal agent.\textsuperscript{18}

### 6.2.5 Bullington Synthesis

This method consists of a $2 + 3$ cycloaddition reaction of methylisocynoacetate with $\alpha,\beta$-unsaturated nitriles 29 to provide a regioselective synthesis of 2-substituted 3,4-dialyl pyrroles 30. The $\alpha,\beta$-unsaturated nitriles used for the reaction was prepared by heating the appropriate benzaldehyde and phenylacetonitrile with either potassium carbonate\textsuperscript{19} or sodium methoxide\textsuperscript{20} in methanol. The facile preparation of $\alpha,\beta$-unsaturated nitriles allows the rapid synthesis of pyrroles with varied substitution patterns. Using this method, Bullington et al. have synthesized an analogue of Furstner intermediate 30 in two steps and have utilized this for the total synthesis of ningalin B 3 (Scheme 5).\textsuperscript{21}

[Scheme 5]

Reagents and conditions: (a) CNCH$_2$COOMe/t-BuOK, 57%; (b) Cs$_2$CO$_3$/DMF, 92%; (c) BBr$_3$/CH$_2$Cl$_2$, -78°C to 25°C, 98%
6.2.6 Gupton’s Method

Gupton has developed novel methods for the synthesis of highly functionalized pyrroles using vinylogous iminium salt derivatives. They have initially utilized the methodology for the total synthesis of lukianol A and more recently for the synthesis of ningalin B hexamethyl ether (Scheme 6).

![Scheme 6](image-url)

Reagents and conditions: (a) DMF-dimethylacetal, DMF, reflux; (b) POCl₃, CH₂Cl₂, reflux; (c) H₂O, THF, rt, E (41%), Z (14%); (d) Glycine Methyl Ester Hydrochloride, DABCO, Toluene, reflux, 92%; (e) NaH, DMF, 80 °C, 70.5%; (f) NaOH, EtOH, H₂O, reflux, 90%; (g) Pb(OAc)₄, EtOAc, reflux, 52%.
The Furstner pyrrole analogue was prepared through a cyclocondensation reaction between β-chloroenal 36 and glycine methyl ester. Although this procedure constructs the compound in three steps from readily available starting materials other analogues would require additional efforts to obtain appropriate starting materials. Kim et al. modified the procedure developed by Gupton and used a vinylogous amide derived from a condensation of DMF-dimethylacetal with commercially available α-(p-methoxyphenyl)-p-methoxyacetophenone for the total synthesis of lamellarin O and lukianol A.25

Synthesis and isolation of various pyrrole-containing marine natural products and related derivatives continue to be a very active area of research given the interesting bioactivity exhibited by such compounds. Our explorative studies on the synthesis of functionalized pyrroles discussed in the previous chapters motivated us to utilize our methods for the synthesis of some pyrrole containing biologically active natural products isolated recently.

6.3 Results and Discussions

6.3.1 Total synthesis of lamellarn O, lamellarn Q, and lukianol A

Our strategy for the synthesis of pyrrole natural products relies on the cyclization of appropriately substituted β-oxoketene-N,S-acetals to form 3,4-diarylpyrrole-2-carboxylates. We have developed a simple regiocontrolled method for the synthesis of 2,3,4,5-tetrasubstituted pyroles 42 and 2,3,5-trisubstituted pyroles 43. Pyrrole 42 was obtained in excellent yield by the cyclization of the ketene-N,S-acetal under Vilsmeier conditions and 43 by the cyclization of the same intermediate in the presence of DBU (Scheme 7). The details of these methods are discussed in Chapter 5 of this thesis.
We were interested in the total synthesis of pyrrole alkaloids such as lamellarin O, lamellarin Q and lukianol A which contain a 3,4-diarylpyrrole-2-carboxylate core. Pyrrole 43 is a promising precursor for these natural products and can be transformed to the 3,4-diaryl pyrrole core by introducing an aryl moiety at 3-position using any of the well known cross-coupling methods followed by desulphurization of the alkylsulphanyl group using Raney nickel. Unfortunately pyrrole 43 was obtained only in moderate yields on cyclization of 41 in the presence of a base such as DBU. Alternatively deformylation or a decarboxylation after oxidation of pyrrole 42 could afford pyrrole 43 which may however increase the number of steps towards the natural products. Thus we thought of methods, which directly afford the pyrrole core of the natural product.

The key feature of the chemistry in the formation pyrrole 42 is the multiple iminoalkylations that could take place prior to the cyclization process. The conversion of the enaminoketone moiety to the chlorosubstituted vinamidium intermediate circumvents the possible stereochemical constraints in the cyclization process. We envisioned that the extension of our pyrrole synthesis from aroyl ketene-N,S-acetals in the presence of Vilsmeier-Haack reagent employing
substituted 2-arylacetophenones could directly lead to 3,4-diarylpyrrole-2-carboxylates.

During the course of our work Gupton et al. have utilized vinylogous amide derived from α-(p-methoxyphenyl)-p-methoxyacetophenone and its analogues for the total synthesis of lukianol A, nigalin B hexamethyl ether and related compounds.\textsuperscript{23, 24} The treatment of the enaminoketone 34 with POC\textsubscript{3} and DMF led to a mixture of E and Z β-chloroenals in moderate yields and only E β-chloroenals can be efficiently converted into pyrrole derivatives resulting in a decreased yield of the natural products. Our intermediate ketene-N,S-acetals have the aminoacetate moiety incorporated prior to the treatment with Vilsmeier reagent, which undergo cyclization directly. Our synthetic strategy towards lamellarin O, lamellarin Q and lukianol A starts from commercially available α-(p-methoxyphenyl)-p-methoxyacetophenone or its isopropyloxy analogue, prepared from the corresponding aldehydes by benzoin condensation followed by deoxygenation.\textsuperscript{26} The retrosynthetic analysis of 3,4-diaryl pyrrole 2-carboxylate is depicted in Scheme 8.

![Scheme 8](image)

Paramethoxy analog 44b was chosen as a model compound for the explorative studies on the total synthesis of the pyrrole natural products. The starting ketone 44b was prepared in 85% yield by the deoxygenation of anizoin using tin and hydrochloric acid. The reaction sequence followed for the synthesis of 3,4-diaryl pyrrole derivatives was same as that for the synthesis of formyl
pyrrole reported in the previous chapter. Thus dithioester derivative 45b was prepared in 94% yield by the reaction of deoxyanizoin 44b in DMF containing sodium hydride and dimethyl trithiocarbonate at 0-10 °C.\(^27\) Benzoin and the isopropoxy analogues of deoxyanizoin (prepared from by the condensation of \(p\)-isopropoxybenzaldehyde in presence of potassium cyanide and deoxygenating the intermediate using tin and hydriodic acid) also afforded the corresponding dithioesters 45a and 45c in excellent yields (Scheme 9). These compounds were characterized with the help of IR, \(^1\)H NMR, \(^13\)C NMR and mass spectra and the details are given in the experimental section.

![Scheme 9](image)

The dithioester 45b was dissolved in dry methanol and glycine methylester hydrochloride (1 equiv.) was added followed by triethyl amine (2 equiv.). The reaction mixture was stirred at room temperature for 4 h and after the completion of the reaction, the product mixture after workup and purification gave the thioamide 46b in 95% yield by column chromatography (Scheme 10).
Scheme 10

The structure of the thioamide 46b was confirmed on the basis of spectral data. The IR spectrum (Fig 1) showed peaks at 3192, 3016, 2959, 1739, 1653, 1597, 1350, 1251, 1170, 1026, 866 and 769 cm⁻¹. The ¹H NMR spectrum (Fig 2) of 46b shows a singlet at δ 3.77 (s, 3H) due to the methyl carboxylate moiety. The methoxy groups on the aromatic rings appeared as singlets at δ 3.81 and 3.85 each integrating to three protons. The methylene group of the aminoacetate appeared as a doublet at δ 4.45 ppm with a coupling constant 3 Hz. The peak at δ 6.26 was due to methynic proton. The aromatic protons appeared as a doublet of doublet at δ 6.90 ppm corresponding to four protons. Another set of doublets appeared at δ 7.44 and δ 8.01 each integrating to two protons. The NH proton appeared as a broad singlet at δ 9.98 ppm. The structure was further confirmed by ¹³C NMR spectrum (Fig 3). The peak at δ 47.65 ppm is due to methyl carbon of the carboxylate group. The aminomethylene carbon appeared at 52.51. The two paramethoxy groups appeared at δ 55.76 and 55.59. The methyne carbon appeared at 65.36. The aromatic carbons appeared at 114.14, 114.77, 127.61, 128.76, 129.34, 129.79, 131.50 ppm. The two paramethoxy group attached carbons on the aromatic ring were at 159.65 and 164.30. The peak at 168.95 was due to the ester carbonyl. The thiocarbonyl group appeared at 199.75 where as the benzoyl carbonyl appeared at δ 196.05 ppm. The
ElMS spectrum (Fig. 4) showed molecular iron peak at m/z 387. Other prominent peaks were at 374, 298, 256, 164, 149, 135 and 107.

Figure 1: IR Spectrum of 46b

Figure 2: $^1$H-NMR Spectrum of 46b
The thioamide 46b undergoes facile methylation when treated with methyl iodide in the presence of potassium carbonate in acetone. Initially the N,S-acetal
was dissolved in acetone and potassium carbonate (3 equiv.) was added. The reaction mixture was refluxed with stirring for 0.5 h and after cooling in an ice bath methyl iodide was added and stirred for 3 hrs. When the reaction was complete, the reaction mixture was poured into ice-cold water, extracted with chloroform and dried using anhydrous sodium sulfate. Evaporation of the organic layer afforded the crude N,S-acetal 47b as a pale yellow glass in 87% yield. Thioamides 46a and 46c also afforded the corresponding N,S-acetals 47a and 47c in excellent yields (Scheme 11). These thioamides were used for further transformations without any purification.

\[
\begin{align*}
46a: & \quad R^1 = H, R^2 = \text{C}_2\text{H}_5 \\
46b: & \quad R^1 = \text{OCH}_3, R^2 = \text{CH}_3 \\
46c: & \quad R^1 = \text{OCH} (\text{C}_2\text{H}_5)_2, R^2 = \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
47a: & \quad R^1 = H, R^2 = \text{C}_2\text{H}_5 & (90\%) \\
47b: & \quad R^1 = \text{OCH}_3, R^2 = \text{CH}_3 & (87\%) \\
47c: & \quad R^1 = \text{OCH} (\text{C}_2\text{H}_5)_2, R^2 = \text{CH}_3 & (85\%)
\end{align*}
\]

**Scheme 11**

Having prepared the ketene-N,S-acetals 47 in respectable yields, we attempted their cyclization under base catalyzed conditions. However the expected 3,4-diarylpyrroles could not be obtained in good yields. Next we have switched over to our well-established Vilsmeier conditions for the cyclization. The N,S-acetals 47 was dissolved in dry DMF and to this was added Vilsmeier-Haack reagent (2 equiv.), keeping the temperature below 10 °C. The reaction mixture was stirred at room temperature for 4h followed by heating at 80 °C for 8h. Work-up using saturated potassium carbonate afforded the diaryl pyrrole -2-carboxylate 48b in 73% yield (Scheme 12).
The structure of 48b was confirmed on the basis of spectral data. The IR spectrum (Fig.5) showed peaks at 3293, 1670, 1608, 1439, 1230, 1035 and 835 cm⁻¹. The ¹H NMR spectrum (Fig.6) shows a peak at δ 2.25 (s, 3H) ppm corresponding to methylsulphanyl group. The methyl carboxylate protons appeared as another singlet at δ 3.74 (s, 3H). The paramethoxy groups appeared as two singlets at δ 3.77 (s, 3H) and δ 3.78 (s, 3H). The aromatic protons appeared as a doublet at δ 6.78 (d, J = 8 Hz, 4H) and another double doublet, at δ 7.06 (d, J = 9 Hz) and δ 7.10 (d, J = 9Hz). The -NΗ proton appeared as a singlet at δ 9.61 (bs, 1H) ppm. The structure was further confirmed by ¹³C NMR spectrum (Fig.7). The methylsulphanyl carbon was at δ 19.13 ppm. The peaks at δ 51.35 and at δ 55.05 are due to the methyl ester and the paramethoxy carbons respectively. The aromatic carbons were at δ 112.87, 113.31, 119.40, 125.05, 126.03, 126.07, 130.85, 131.41, 131.83, and 132.23. The methoxy group attached carbons of the aromatic rings appeared at δ 158.17 and 158.41. The peak at δ 161.06 ppm was due to carbonyl carbon of the carboxylate group. EIMS spectrum (Fig.8) showed the molecular ion peak at m/z 383 (100 %). Other prominent peaks were at 351, 292, 276, 238, 223 and 135.
Figure 5: IR Spectrum of 48b

Figure 6: $^1$H-NMR Spectrum of 48b
Figure 7: $^{13}$C-NMR Spectrum of 48b

Figure 8: Mass Spectrum of 48b
The validity of this 3,4-diaryl pyrrole synthesis was further evaluated by performing the Vilsmeier reaction on functionalized ketene N.S acetals 47a and 47c. The corresponding 3,4 diaryl pyroles 48a and 48c were formed in 78% and 71% yields respectively under similar conditions (Scheme 12). The structures of these pyroles also were confirmed with the help of $^1$H NMR, $^{13}$C NMR and mass spectra. The spectral data of these compounds are given in the experimental section. The pyrrole 48c was prepared with a view to synthesize lamellarin O, as the isopropyl group can easily be deprotected under mild conditions.28

Thus we have prepared the pyrrole 48b from dithioester 45b derived from commercially available deoxyanisoin in four steps with overall yield of 51%. The pyrrole is very similar in structure to the pyrrole core in the natural products. It contains a removable alkyl sulphanyl group at 5 position. Removal of methyl sulphanyl group from 48b could afford the Furstner intermediate 11.

Being synthesized the pyrrole 48b our next task was to check the feasibility of desulfurisation. Reductive removal of the methylthiogroup from aromatic ring could be possible with the help of Raney-Ni.29 The pyrrole 48b (10 mmol) was dissolved in absolute ethanol and freshly prepared Raney-Ni (W5, 5 times by weight) was added. The suspension was refluxed with stirring for three hours and after the reaction was complete (monitored by TLC), the solvent was evaporated under reduced pressure. The residue was filtered through a short column packed with silica gel using hexane-ethyl acetate to give the Furstner intermediate 11 as a white crystalline solid in 74% yield (Scheme 13). The melting point of the compound was in agreement with the reported value. The structure of this compound was confirmed with the help of $^1$H NMR $^{13}$C NMR and mass spectral data which was in good agreement with the reported values. Furstner used this intermediate for the first total synthesis of lukianol A and lamellarin O dimethyl ether. Different groups have later targeted the same or a similar intermediate for
the total synthesis of lamellarin O and related alkaloids. Desulfurisation of pyrrole 48c afforded the corresponding pyrrole 49a and its structure was confirmed with the help of $^1$H NMR, $^{13}$C NMR and mass spectral data, which are given in the experimental section.

Scheme 13

The Furstner intermediate can be transformed into the natural products lamellarin Q and lukianol A in excellent yields by literature procedures. Thus on treating the intermediate with BBr$_3$ affords lamellarin Q in a single step where as alkylation using paramethoxy phenacyl bromide followed hydrolysis in the presence of lithium hydroxide and subsequent lactonisation affords lukianol A (Scheme 14).
As the protecting group can easily be removed under mild conditions using AlCl₃, the isopropyl analogue 49a can be used for the synthesis of lamellarin. However, one problem associated with this protecting group was that the products were separated as oily liquids and special care was needed while purification. The pyrrole was first alkylated using paramethoxy phenacyl bromide by refluxing in acetone containing potassium carbonate (3 mmol) for twelve hours in 88% yield, a procedure similar to that reported for the synthesis of lukianol A. The diisopropoxy lamellarin 50 was separated as a pale yellow glass. This compound could be transformed into the unstable lamellarin O in 95% yield by removing the isopropoxy group using AlCl₃ in dichloromethane (Scheme 15).

![Scheme 15](image)

6.3.2 **Efforts on a total synthesis of rigidin**

Rigidin 6 is a pyrrolopyrimidine alkaloid isolated in 1990 by Kobayshi et al. that can inhibit calmodulin activated brain phosphodiesterase. Only two total synthesis of this molecule have been reported till date and both methods start with pyrimidine ring and construction of the pyrrole ring and aroyl group at a later stage.  

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Prepared by BeeHive Digital Concepts Cochin for Mahatma Gandhi University Kottayam
Our strategy for the synthesis of rigidin 6 starts with the N,S-acetal 51b derived from β-oxothiol ester 52b (Scheme 16).

We have developed a highly efficient synthesis of β-oxothiolesters 52 by the partial hydrolysis of α-oxoketene dithioacetals using bromine supported on polyvinyl pyrrolidone (see Chapter 3). The thiolester 52a on reaction with phenyl isothiocyanates (1 equiv.) followed by alkylation using methyl iodide afforded a mixture of ketene N,S-acetals 53a and 54a in 47% and 36% yields respectively (Scheme 17). During the course of the reaction a second molecule of phenyl isothiocyanate was added to the initially formed N,S-acetal 53a followed by methylation affords the intermediate 54b. This undergoes a methyl shift from sulphur to nitrogen during the reaction workup affording 54a. Thus when the thiol ester 52a was reacted with excess phenyl isothiocyanate, 54a was formed in 68% yield. Reaction of 52b also afforded 53b in good yields. We anticipated that pyrrole ring of rigidin can be synthesized from the ketene N,S-acetal 53 by N-alkylation using p-methoxyphenacyl bromide followed by cyclization. On the other hand pyrimidine ring can be constructed by condensation of 53 with urea.
Condensation of \( \alpha \)-oxo ketene-N,S-acetals with urea 55 or its derivatives is a common method for preparing compounds like 56. However our efforts to condense 53 with urea and its derivatives could not afford the pyrimidine 56 (Scheme 18).

We have also attempted the condensation of 54a with urea but it underwent a methyl shift followed by the elimination of a molecule of phenylisothiocyanate on heating above 100 °C producing N-methyl derivative 57 (Scheme 19).
Base catalyzed reaction of the thiolester 52b with benzylisothiocyanate using potassium carbonate in DMF led to the thioamide 58 in low yield (Scheme 20). Attempted condensation of 58 with urea also failed to form the corresponding pyrimidine derivative.

We have also prepared the ketene dithioacetal 59 from the thiolester 52a in 52% yield by reacting it with carbon disulphide in the presence of potassium carbonate in DMF. We envisaged that condensation of the ketene dithioacetal 59 with urea could afford the methyl sulfanyl functionalized pyrimidine. However on refluxing the ketene dithioacetal 59 with urea in presence of sodium ethoxide in ethanol for 2 h, the deacylated product 60 was formed (Scheme 21).
Ley et al. have synthesized tetronic acid and related natural products by the condensation of thiolesters with secondary amines in presence of silver trifluoroacetic acid, a thiophilic metal salt, in aprotic solvents like dichloromethane. However attempted condensation of the N,S-acetal with urea in presence of silver trifluoroacetate could not afford the corresponding pyrimidine derivative. This may be due to the poor solubility of urea in the reaction medium. The problem has been solved by using the dibenzyl derivative of urea 61, which is homogeneous in dichloromethane.

Thus to the N,S-acetal 51a and dibenzyl urea 61 in dichloromethane, silver trifluoroacetate was added and the mixture was stirred at room temperature for 10 minutes. The voluminous precipitate formed was allowed to settle and the solvent was decanted. The precipitate was washed using excess dichloromethane and again decanted. The combined solvents were evaporated and filtered through a short silica gel column to afford yellow viscous oil in 68% yield. Based on spectral data the compound has been identified as 6-anilino-5-benzoyl-1,3-dibenzyl-2,4(1H,3H)-pyrimidinedione 62 (Scheme 22).
The IR (KBr) spectrum showed bands at 1720, 1661 and 1566 cm⁻¹. The \(^1\)H NMR spectrum (CDCl₃, 300 MHz) of 62 shows a sharp four proton singlet at δ 4.12 ppm due to benzylic protons. The aromatic protons appear as a multiplet between δ 7.10 and 7.67 ppm integrated to twenty protons. The NH proton appears as a broad singlet at δ 9.30 ppm. The structure was further confirmed by \(^{13}\)C NMR spectrum (75.47 MHz, CDCl₃). The peak at δ 45.84 ppm is due to benzylic carbons. Aromatic carbons show peaks at δ 120.57, 120.72, 129.00, 129.97, 134.79, 136.43 and 137.93 ppm. The number of peaks is less than in the \(^{13}\)C NMR spectrum expected due to the possible overlap of several aromatic carbons. One of the carbonyl groups of the pyrimidine ring gave a peak at δ 164.07 where as the phenacyl carbonyl carbon at δ 196.95 ppm. The mass spectrum (GCMS) showed the molecular ion peak at 487. Other prominent peaks were at 395, 366, 254, 239 and 105.

N-alkylation of 62 using phenacyl bromide followed by cyclisation of the amino pyrimidine could afford pyrrolopyrimidine, the ring system found in rigidin (Scheme 23). However our attempts to alkylate 62 with phenacyl bromide under different conditions did not afford the desired product 63.

![Scheme 23](image)

In conclusion, we have developed efficient methods for the formal total synthesis of several biologically active pyrrole containing natural products. The method is simple, less expensive, and very general so that many more analogues of these natural products can be synthesized from appropriately substituted deoxybenzoins. Even though our efforts towards the total synthesis of marine
natural product rigidin could not be completed we have proposed a simple alternative pathway towards it. Efforts are going on in our laboratory towards the realization of this goal with appropriate modifications.

6.4 Experimental

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. IR spectra were recorded on Shimadzu IR-470, JASCO FT/IR-5300 or ABB Bomem MB 104 spectrometer and the frequencies are reported in cm⁻¹. Proton NMR spectra were recorded on a Bruker DRX-300 (300 MHz) or on a Bruker amx 400 (400 MHz) spectrometer in CDCI₃. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Coupling constants J are given in Hz. The Electron Impact Mass Spectra were obtained on a Finnigen-Mat 312 instrument and FAB mass spectra on a Jeol SXS-102 instrument. The GCMS mass spectra were obtained on a GCMS-Shimadzu 5050 model instrument.

6.4.1 General procedure for the synthesis of dithioesters 45

Sodium hydride (50% suspension in mineral oil, 0.96 g, 20 mmol) was washed with anhydrous petroleum ether and suspended in anhydrous DMF. The reaction mixture was kept in an ice water and the ketone 44 (10 mmol) was added to it. Stirred for 0.5 h and allowed to attain room temperature. The reaction mixture was poured over crushed ice and extracted with diethyl ether (3x50 mL). The organic layer was washed with water and dried using anhydrous sodium sulphate. The solvent was removed in vacuum and the crude product was purified by passing through a short column of silica gel using hexane.
Methyl 3-oxo-2,3-diphenylpropanedithioate 45a was obtained by the reaction of 2-phenylacetophenone (3.9 g, 20 mmol) with dimethyl trithiocarbonate (2.7 g, 20 mmol) as yellow crystalline solid. Yield 5.4 g (96 %), mp 128-130 °C. IR (KBr) ν max/cm⁻¹ = 1693, 1446, 1282, 1140, 958, 827. ¹H NMR (300 MHz, CDCl₃) δ 2.6 (s, 3H, SCH₃), 6.49 (s, 1H, CH), 7.25-7.55 (m, 6H, aromatic) and 7.99 (d, 4H, aromatic) ppm.; ¹³C NMR (75.47 MHz, CDCl₃) δ 20.55 (S(CH₃), 73.25 (CH), 128.42, 128.80, 128.99, 129.76, 133.39, 135.32, 136.42 (aromatic), 193.40 (thiocarbonyl), and 232.20 (carbonyl) ppm.; EIMS m/z (%) 286 (M⁺, 4), 238 (10), 178 (10), 165 (6), 134 (48), 121 (4), 105 (100).

Methyl 2,3-bis(4-methoxyphenyl)-3-oxopropanedithioate 45b was obtained by the reaction of 2-(4-methoxyphenyl)-4-methoxyacetophenone (5.1 g, 20 mmol) with dimethyl trithiocarbonate (2.7 g, 20 mmol) as yellow glass. Yield 6.5 g (94 %). ¹H NMR (400 MHz, CDCl₃) δ 2.56 (s, 3H, SCH₃), 3.79 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 6.34 (s, 1H, CH) and 6.58-7.98 (m, 8H, aromatic) ppm; ¹³C NMR (75.47 MHz, CDCl₃) δ 20.47 (S(CH₃), 55.27 (OCH₃), 55.49 (OCH₃), 72.27 (CH), 113.76, 114.14, 129.27, 130.87, 131.31, 132.21, 159.65, 163.05 (aromatic), 192.43 (C=O) and 233.76 (C=S) ppm; EIMS m/z (%) 346 (M⁺, 7), 298 (12), 211 (15), 186 (23), 164 (15), 135 (100).
Methyl2,3-bis(4-isopropoxyphenyl)-3-oxopropanedithioate

45c was obtained by the reaction of 2(4-isopropoxyphenyl)-4-isopropryacetophenone (8 g, 20 mmol) with dimethyl trithiocarbonic (2.7 g, 20 mmol) as yellow glass. Yield 7.3 g (92%). IR (KBr) ν<sub>max</sub>/cm<sup>-1</sup> = 2974, 2924, 1896, 1682, 1601, 1176, 952, 814. ¹H NMR (400 MHz, CDCl₃) δ 1.21-1.39 (m, 12H, CH₆), 2.60 (s, 3H, SCH₃), 4.52 (sept, 1H, J = 6 Hz, CH(CH₃)₂), 4.64 (sept, 1H, J = 6 Hz, CH(CH₃)₂), 4.68 (s, 1H, CH), 6.85 (m, 4H, aromatic), 7.40 (d, 2H, J = 8 Hz, aromatic) and 7.98 (d, 2H, J = 8 Hz, aromatic) ppm; ¹³C NMR (400 MHz, CDCl₃) δ 20.50 (SCH₃), 21.98, 22.15(CH(CH₃)₂), 69.88 (CH(CH₃)₂), 70.24 (CH(CH₃)₂), 72.32 (CH), 115.29, 115.79, 127.42, 128.89, 130.89, 131.39, 158.06, 162.28 (aromatic), 192.29 (carbonyl), 233.88 (thiocarbonyl) ppm; EIMS m/z (%) 402 (M⁺,3%), 354 (10), 242 (15), 163 (48), 121 (100).

6.4.2 General procedure for the synthesis of β-oxothioamides 46

The β-oxodithioesters 45 obtained in the previous experiment (10 mmol) was dissolved in appropriate dry alcohol and glycine ester hydrochloride (10mmol) was added to it at room temperature. Triethylamine (20 mmol) was added to it and the reaction mixture was stirred at room temperature for 4 hours. It was then added to crushed ice and extracted with chloroform (3x50 mL). The organic layer was washed with water, dried over anhydrous Na₂SO₄ and evaporated to afford the crude product. It was chromatographed over silica gel using hexane:ethylacetate (7:3) as eluent to give the thioamides 46 in excellent yields.
Ethyl 2-[(3-oxo-2,3-diphenylpropanthioyl)amino] acetate 46a was obtained by the reaction of methyl 3-oxo-2,3-diphenylpropanedithioate 45a (2.8 g, 10 mmol) with glycine ethylester hydrochloride (1.4 g, 10 mmol) in dry ethanol as yellow glass. Yield 3.3 g (98%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.23-1.32 (m, 3H, \(\text{CH}_2\text{SH}\)), 4.15-4.45 (m, 4H, \(\text{OCH}_2\), and \(\text{NHCH}_2\)), 6.38 (s, 1H, \(\text{CH}\)), 7.27-7.60 (m, 8H, aromatic), 8.02 (d, 2H, \(J = 8\) Hz, aromatic), 9.70 (s, 1H, \(\text{NH}\) ppm; \(^1\)C NMR (75.47 MHz, CDCl\(_3\)) \(\delta\) 14.1, 47.98 (\(\text{OCH}_2\) (C)), 61.88 (\(\text{OCH}_2\) (C)), 66.88 (CH), 128.07, 128.58, 128.89, 129.08, 129.21, 134.06, 135.05, 136.04 (aromatic), 168.43 (ester carbonyl), 197.46 (carbonyl) and 198.48 (thiocarbonyl) ppm; EIMS m/z (%) 341 (M\(^+\) 6), 236 (3), 203 (61), 162 (15), 134 (21), 118 (6), 105 (100).

Methyl 2-[(2,3-bis(4-methoxyphenyl)-3-oxopropanthioyl)amino]acetate 46b was obtained by the reaction of methyl 2,3-bis(4-methoxyphenyl)-3-oxopropanedithioate 45b (3.4 g, 10 mmol) with glycine methyl ester hydrochloride (1.5 g, 10 mmol) as yellow glass. Yield 3.6 g (95%). IR (KBr) \(\nu_{\text{max}}/\text{cm}^{-1} = 3192, 3016, 2959, 1739, 1653, 1597, 1350, 1251, 1170, 1026, 866, 769. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.77 (s, 3H, \(\text{CO}_2\text{CH}_3\)), 3.81 (s, 3H, ArOCH\(_3\)), 3.85 (s, 3H, ArOCH\(_3\)), 4.45 (d, 2H, \(J = 3\) Hz, NHCH\(_2\)), 6.26 (s, 1H, \(\text{CH}\)), 6.90 (m, 4H, aromatic), 7.48 (d, 2H, \(J = 6\) Hz, aromatic), 8.01 (d, 2H, \(J = 6\) Hz, aromatic), 9.98
Methyl 2-{f2.3-bis(4-isopropoxyphenyl)-3-oxopropanethioyljamino)acetate 46c was obtained by the reaction of methyl 2,3-bis(4-isopropoxyphenyl)-3-oxopropanedithioate 45c (4 g, 10 mmol) as yellow glass. Yield 4.1 g (94%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.20-1.38 (m, 12H, CH (CH$_3$)$_2$), 3.79 (s, 3H, CO$_2$CH$_3$); 4.42 (m, 2H, NCH$_2$), 4.48 (sept, 1H, $J$ = 6Hz, CH (CH$_3$)$_2$), 4.63 (sept, 1H, $J$ = 6Hz, CH(CH$_3$)$_2$), 6.24 (s, 1H, CH), 6.83 (d, 2H, $J$ = 8Hz, aromatic), 7.41 (d, 2H, $J$ = 8 Hz, aromatic), 7.98 (d, 2H, $J$ = 8 Hz, aromatic). 9.85 (bs, 1H, NH) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 21.88 (CH(CH$_3$)$_2$), 22.03 (CH(CH$_3$)$_2$), 47.73 (NHCH$_2$), 52.54 (CO$_2$CH$_3$), 65.33 (CH), 69.93 (CH(CH$_3$)$_2$), 70.36 (CH(CH$_3$)$_2$), 115.38, 116.45, 127.29, 128.35, 129.16, 131.58, 158.07, 162.92 (aromatic), 168.97 (ester carbonyl), 196.13 (carbonyl) and 199.79 (thiocarbonyl) ppm; EIMS m/z (%) 443 (M$^+$ 6), 409 (4), 369 (3), 228 (6), 192 (8), 163 (54), 121 (100).

(bs, 1H, NH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 47.65 (NH(H$_2$)), 52.51 (CO$_2$CH$_3$), 55.23 (OCH$_3$), 55.59 (OCH$_3$), 65.36 (CH), 114.14, 114.77, 127.61, 128.76, 129.34, 131.51, 159.65, 164.30 (aromatic), 168.95 (ester carbonyl), 196.05 (carbonyl), 199.75 (thiocarbonyl) ppm; EIMS m/z (%) 387 (M$^+$ 15), 374 (8), 298 (5), 256 (10), 227 (7), 192 (15), 164 (31), 149 (4), 135 (100).

\[\text{Methyl 2-\{f2.3-bis(4-isopropoxyphenyl)-3-oxopropanethioyljamino)acetate 46c}\]
6.4.3 General procedure for the synthesis of ketene-N,S-acetals 47

The thioamide 46 (10 mmol) was dissolved in dry acetone and anhydrous potassium carbonate (30 mmol) was added. The reaction mixture was refluxed for 30 minutes with stirring and was then cooled in an ice bath. Methyl iodide was added slowly to the reaction mixture and was stirred for another four hours. The mixture was added to ice-cold water and extracted with dichloromethane (2x50 mL). The organic layer was washed with water, dried over anhydrous Na₂SO₄ and evaporated to afford the crude N,S-acetal 47 in excellent yields, which were used for further transformations without purification.

6.4.4 General Procedure for the Synthesis of 3,4-Diarylpyrrolecarboxylates 48

The Vilsmeier reagent was prepared by mixing ice cold, dry DMF (25 mL) and POCl₃ (2mL, 20 mmol). The mixture was then stirred for 30 minutes at room temperature. The N,S-acetal 47 (3.25g, 10 mmol) was dissolved in dry DMF (10 mL) and added to the Vilsmeier reagent over 10 minutes at 0-5 °C. The reaction mixture was stirred for 6 hours at room temperature and was heated at 80 °C for 1 h with stirring. The mixture was then cooled and poured into cold, saturated aq. K₂CO₃ (200 mL) and extracted with diethyl ether (3x50 mL). The organic layer was washed with water, dried over anhydrous Na₂SO₄ and evaporated to afford the crude product, which was chromatographed over silica gel using hexane ethylacetate (4:1) as eluent to give alkyl-3,4-diaryl-5-(alkylsulfanyl)-1H-pyrrole-2-carboxylates 48.
Ethyl 5-(methylsulfanyl)-3,4-diphenyl-1H-pyrrole-2-carboxylate 48a was obtained by the Vilsmeier reaction of ethyl 2-\{[(E)-1-(methylsulfanyl)-3-oxo-2,3-diphenyl-1-propenyl]amino\}acetate 47a (3.5 g, 10 mmol) as white crystalline solid. Yield 2.6 g (78%), mp 147-148 °C. $^1$H NMR (300 MHz, CDCl₃) δ 1.15 (t, 3H, $J$ = 7 Hz, OCH₂CH₃), 2.26 (s, 3H, SCH₂), 4.20 (q, 2H, $J$ = 7 Hz, OCH₂CH₃), 7.19 (m, 10H, aromatic) ppm; $^{13}$C NMR (75.47 MHz, CDCl₃) δ 14.46 (CH₂CH₃), 19.69 (SCH₂), 60.82 (CH₂CH₃), 120.48, 125.50, 126.88, 127.15, 127.65, 128.16, 130.14, 130.76, 131.23, 131.41, 134.05, 134.34 (aromatic) and 161.15 (ester carbonyl) ppm; EIMS m/z (%) 337(M⁺, 74), 323 (30), 291 (39), 262 (50), 246 (20), 230 (100), 221 (10), 203 (10), 189 (24), 178 (18), 165 (8), 145 (11), 139 (3).

Methyl 3,4-bis(4-methoxyphenyl)-5-(methylsulfanyl)-1H-pyrrole-2-carboxylate 48b was obtained by the Vilsmeier reaction of methyl 2-\{[(E)-2,3-bis(4-methoxyphenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino\}acetate 47b (4 g, 10 mmol) as white crystalline solid. Yield 2.8 g (73%), mp 180-181 °C. IR (KBr) ν$_{max}$/cm⁻¹ = 3293, 1670, 1608, 1439, 1230, 1035, 835. $^1$H NMR (300 MHz, CDCl₃) δ 2.25 (s, 3H, SCH₂), 3.74 (s, 3H, CO₂CH₃), 3.77 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 6.78 (d, $J$ = 8 Hz, 4H, aromatic), 7.09 (m, 4H, aromatic) ppm; $^{13}$C NMR (75.47 MHz, CDCl₃) δ...
19.13 (SCH₃), 51.35 (CO₂CH₃), 55.05 (OCH₃),
112.87, 113.31, 119.40, 125.05, 126.03, 126.07,
130.85, 131.41, 131.83, 132.23, 158.17, 158.41
(aromatic) and 161.06 (ester carbonyl) ppm; EIMS
m/z (%) 383(M⁺, 100), 351 (63), 292 (54), 276(52),
238(18), 223 (24), 135 (47).

Methyl3.4-bis(4-isopropoxyphenyl)-5-
(methylsulfanyl)-1H-pyrrole-2-carboxylate 48c was
obtained by the Vilsmeier reaction of methyl 2-{(E)-
2,3-bis(4-isopropoxyphenyl)-1-(methylsulfanyl)-3-
oxo-1-propenyl]amino}acetate 47c (4.5 g, 10 mmol)
as pale yellow glass. Yield 3.1 g (71 %). ¹H NMR (400
MHz, CDCl₃) δ 1.32 (m, 12H, CH(CH₃)₂), 2.24 (s, 3H,
SCH₃), 3.74 (s, 3H, methyl ester), 4.52 (m, 2H,
CH(CH₃)₂) 6.75 (m, 4H, aromatic), 7.04 (m, 4H,
aromatic), 9.15 (bs, 1H, NH) ppm; ¹³C NMR (100
MHz, CDCl₃) δ 19.26 (SCH₃), 22.15 (CH(CH₃)₂),
51.35 (CO₂CH₃), 69.80 (CH(CH₃)₂), 111.56, 113.84,
114.25, 114.87, 115.21, 115.64, 125.12, 126.23,
131.48, 131.92, 157.45, 158.62 (aromatic) and 162.25
(ester carbonyl) ppm. EIMS m/z (%) 439(M⁺, 18),
407 (8), 395 (6), 353 (12), 323 (13), 294 (12), 248
(16), 234 (14), 210 (24), 163 (67) and 121 (100).
6.4.5 General procedure for reductive dethiomethylation of pyrrole 48 using Raney-Ni.

To a solution of pyrrole 48 (10 mmol) in ethanol (25mL) was added Raney-Ni (W5.5 times by weight), and the suspension was refluxed with stirring for 3 h. After the reaction was complete (monitored by TLC), the solvent was filtered, evaporated under vacuum to give the crude products 49a which were purified by passing through a short column packed with silica gel using hexane-EtOAc (4:1) as eluent.

Methyl 3,4-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate 11 (0.66 g, 2 mmol) was obtained by the desulphurization reaction of methyl 3,4-bis(4-methoxyphenyl)-5-(methylsulfonyl)-1H-pyrrole-2-carboxylate 3.8 g, (10 mmol) 48b using Raney-Ni as pale yellow crystalline solid identical in all compared respects with authentic material. Yield 2.5 g (74%), mp 170-172 (lit. 8 mp 169-171 °C). \(^1\)HMR (CDCl\(_3\), 300 MHz) 3.72 (s, 3H, CO\(_2\)CH\(_3\)), 3.76 (s, 3H, OCH\(_3\)), 3.81 (s, 3H, OCH\(_3\)), 6.74 (d, 2H, \(J = 8\) Hz, aromatic), 6.84 (d, 2H, \(J = 8\) Hz, aromatic), 7.00-7.03 (m, 3H, aromatic), 7.18 (d, 2H, \(J = 8\) Hz, aromatic), 9.25 (bs, 1H, NH). \(^13\)C NMR (CDCl\(_3\), 75.47 MHz, CDCl\(_3\)) δ 51.2, 55.2, 55.2, 113.6, 113.8, 119.3, 120.1, 126.4, 127.1, 129.4, 131.8, 158.0, 158.5, 161.6, ppm; GCMS m/z (%) 337 (M\(^+\), 45), 306 (22), 305 (100), 290 (15), 263 (7), 234 (10), 203 (7), 191 (19), 164 (7), 152 (14).
Methyl 3,4-bis(4-isopropoxyphenyl)-1H-pyrrole-2-carboxylate 49a was obtained by the desulphurization reaction of methyl 3,4-bis(4-isopropoxyphenyl)-5-(methylsulfanyl)-1H-pyrrole-2-carboxylate 48c 4.3 g (10 mmol) as pale yellow glass. Yield 2.8 g (72%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.32 (m, 12H, CH(CH\(_3\))\(_2\)); 3.72 (s, 3H, CO\(_2\)CH\(_3\)); 4.51 (m, 2H, CH(CH\(_3\))\(_2\)); 6.72 (d, 2H, \(J = 8\) Hz, aromatic), 6.82 (d, 2H, \(J = 8\) Hz, aromatic), 7.00 (d, 2H, \(J = 8\) Hz, aromatic), 7.17 (d, 2H, \(J = 8\) Hz, aromatic), 9.22 (s, 1H, NH) ppm; \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 22.13, 51.19, 69.87, 115.12, 115.64, 116.54, 120.13, 126.8, 127.02, 128.92, 129.47, 131.92, 156.93, 161.68, ppm; EIMS m/z (%) 393 (M\(^+\), 4), 361 (11), 319 (15), 277 (100), 220 (22), 165 (21), 121 (25).

Methyl 3,4-bis(4-isopropoxyphenyl)-1-{(4-methoxyphenyl) (oxo)ethyl}-1H-pyrrole-2-carboxylate 50 was obtained by the reaction of methyl 3,4-bis(4-isopropoxyphenyl)-1H-pyrrole-2-carboxylate 49a 4g (10 mmol) with \(p\)-methoxyphenacylbromide in acetone containing potassium carbonate at room temperature for 12 h as a pale yellow glass. Yield 4.7 g (88%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.22-1.38 (m, 12H, CH(CH\(_3\))\(_2\)); 3.97 (s, 3H, methyl ester); 3.98 (s, 3H, OCH\(_3\)); 4.85 (m, 2H, CH(CH\(_3\))\(_2\)); 4.81 (s, CH\(_2\)); 6.55-7.04 (m, 6H, aromatic), 7.54-8.18 (m, 6H, aromatic) ppm. \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 29.60 (CH(CH\(_3\))\(_2\)); 55.54 (CO\(_2\)CH\(_3\)); 56.25 (OCH\(_3\)); 56.56 (CH\(_2\)); 69.63 (CH(CH\(_3\))\(_2\)); 111.06, 114.48, 113.87, 114.20, 126.42, 128.87, 129.38, 130.01, 130.25, 130.70, 131.18, 134.07, 153.68, 154.27, 160.19 (aromatic), 164.21 (ester carbonyl), 195.93 (carbonyl) ppm; EIMS m/z (%) 541 (M\(^+\), 8), 522 (11), 506 (5), 428 (7), 387 (25), 353 (21), 309 (70), 295 (31), 280 (18), 213 (55), 177(31), 135 (100), 121(28).
6.4.6 General procedure for the preparation of ketene S,N-acetal 53

β-Oxothioester 52 (10 mmol) was dissolved in dry DMF (20 mL). To this was added anhydrous potassium carbonate (30 mmol) followed by aryl isothiocyanate (10 mmol). The reaction mixture was stirred at room temperature 4h. Methyl iodide was added to the reaction mixture and stirring was continued for 4h. When the reaction was complete (TLC), the mixture was poured into ice-cold water and extracted using chloroform (2 x 50 mL). The organic layer was washed with water, dried (Na₂SO₄) and evaporated to afford a yellow viscous oil which was purified by passing through a silica gel column using hexane ethyl acetate (7:3) as eluent.

\[
\text{S-Methyl(Z)-3-anilino-2-benzoyl-3-(methylsulfanyl)-2-propanethioate 53a}
\]

was obtained as a pale yellow liquid by the reaction of S-methyl-3-oxo-3-phenylpropanethioate 52a 1.9 g (10 mmol) with phenyl isothiocyanate 2g (15 mmol) in presence of anhydrous potassium carbonate in DMF and subsequent alkylation using methyl iodide. Yield 1.5 g (47%). \( ^1H \text{ NMR (300 MHz, CDCl}_3 \) δ 1.81 (s, 3H, \( \text{SCH}_3 \)), 2.24 (s, 3H, \( \text{SCH}_3 \)), 7.17-7.94 (m, 10H, aromatic), 12.08 (bs, 1H, \( \text{NH} \)) ppm. EIMS m/z (%) 343 (M⁺(24)), 295 (65), 246 (27), 219 (12), 144 (32), 105 (100).
S-Methyl(Z)-3-(benzylamino)-2-(4-methoxybenzoyl)-3-(methylsulfanyl)-2-propanethioate 53b was isolated as a pale yellow liquid by the reaction of S'-methyl-3-(4-methoxyphenyl)-3-oxopropanethioate 52b (2.2 g, 10 mmol) with benzyl isothiocyanate (10 mmol) in presence of anhydrous potassium carbonate in DMF and subsequent alkylation using methyl iodide. Yield 2.2 g (58%). 1H NMR (300 MHz, CDCl₃) δ 2.15 (s, 3H, SCH₃), 2.21 (s, 3H, S(CH₃), 3.83 (s, 3H, OCH₃), 4.72 (s, 2H, CH₂), 6.68-8.07 (m, 9H, aromatic), 10.79 (bs, 1H, NH) ppm.

S-Methyl(Z)-2-benzoyl-3-[(methylamino) carbothioyl anilino]-3-(methylsulfanyl)-2-propanethioate 54a was obtained as a pale yellow oil by the reaction of S-methyl-3-oxo-3-phenylpropanethioate 52a (1.9 g, 10 mmol) with phenyl isothiocyanate 2g (1.5 mmol) in presence of anhydrous potassium carbonate in DMF and subsequent alkylation using methyl iodide. Yield 1.7 g (36%). 1H NMR (300 MHz, CDCl₃) δ 2.10 (s, 3H, SCH₃), 2.20 (s, 3H, SMe), 3.44 (s, 3H, N-CH₃), 7.08-7.65 (m, 15H, aromatic) ppm. 13C NMR (75.47 MHz, CDCl₃) δ 12.2, 17.7 (SCH₃), 45.1 (N-CH₃), 115.2, 122.7, 123.2, 126.6, 128.0, 128.2, 128.8, 129.2, 129.3, 129.7, 131.6, 133.9, 140.8, 145.1, (aromatic), 178.0 (thioamide), 187.3 (ester carbonyl) and 190.8 (carbonyl). FAB MS m/z (%) 492 (M⁺ (7)), 460 (10), 431 (10), 391 (42), 358 (84), 310 (100), 282 (25), 262 (27), 209 (20), 165 (34), 149 (67).
S-Methyl(Z)-2-benzoyl-3-(methylanilino)-3-(methylsulfanyl)-2-propenethioate 57 was obtained as a white crystalline solid by heating S-Methyl(Z)-2-benzoyl-3-{[(methylanilino)carbothioyl]anilino}-3-(methylsulfanyl)-2-propanethioate 54a (4.9 g, 10 mmol) at 100 °C in DMF for 4 h followed by usual work up. Yield 3.4 g (96%), mp 100-102 °C. IR \( \nu_{\text{max}}/\text{cm}^{-1} \) 3036, 2922, 1652, 1621, 1588, 1367, 1253, 1099. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.90 (s, 3H, SCH\(_3\)), 1.93 (s, 3H, SCH\(_3\)), 3.37 (s, 3H, NCH\(_3\)), \( \delta \) 7.21-7.79 (m, 10H, aromatic) ppm. \(^13\)C NMR (75.47 MHz, CDCl\(_3\)) \( \delta \) 16.6, 16.9 (SCH\(_3\)), 36.8 (N-CH\(_3\)), 126.3, 127.1, 128.1, 128.5, 129.3, 132.6, 137.6, 142.7 (aromatic), 165.9 (ester carbonyl), 192.1 (carbonyl). EIMS m/z (%): 357 (M\(^+\) (15)), 309 (5), 251 (83), 250 (50), 204 (6), 105 (100).

### 6.4.7 General procedure for the preparation of thioamide 58

\( \beta \)-Oxothiolester 52b (10 mmol) was dissolved in dry DMF (20 mL). To this was added anhydrous potassium carbonate (30 mmol) followed by benzyl isothiocyanate (10 mmol). The reaction mixture was stirred at room temperature 10h. The mixture was poured into ice cold water and extracted using chloroform (2 x 50 mL). The organic layer was washed with water, dried (Na\(_2\)SO\(_4\)) and evaporated to afford yellow solid, which was purified by passing through a silica gel column using hexane ethyl acetate (7:3) as eluent.
S-Methyl(Z)-3-(benzylamino)-2-(4-methoxybenzoyl)-3-sulfanyl-2-propenethioate 58 was obtained as a yellow crystalline solid by the reaction of S-methyl-3-(4-methoxyphenyl)-3-oxopropanethioate 52b (2.1 g, 10 mmol) with benzyl isothiocyanate 1.4 g (10 mmol) in presence of anhydrous potassium carbonate in DMF. Yield 0.6 g (18%). mp 136-137 °C. IR $v_{\text{max}}$/cm$^{-1}$ 1639, 1599, 1507, 1361, 1253, 1171 and 1021. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.67 (s, 3H, SCH$_3$), 3.84 (s, 3H, OCH$_3$), 5.13 (s, 2H, CH$_2$), 6.94-8.27 (m, 9H, aromatic) ppm. $^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta$ 15.71, (SCH$_3$), 49.40 (CH$_2$), 55.19 (OCH$_3$), 102.29, (methynic), 112.79, 128.24, 128.39, 128.72, 129.89, 131.20, 133.15, 159.00 (aromatic), 162.28 (thiocarbonyl), 172.85 (thiolester carbonyl) and 183.67 (carbonyl).

6.4.8 Reaction of $\beta$-oxoketene S-S-acetal 59 with sodium ethoxide

$\beta$-Oxoketene S-S-acetal 59 (10 mmol) was dissolved in absolute ethanol (20 mL). To this was added urea (10 mL) followed by sodium ethoxide (2 equiv.). The reaction mixture was refluxed for 2 h. After the completion of the reaction the mixture was cooled and poured into ice-cold water and extracted using chloroform (2 x 50 mL). The organic layer was washed with water and dried using sodium sulphate. Evaporation of the solvent afforded an yellow oil which was purified by passing through a short silicagel column using hexane ethylacetate (4:1) as eluent.
2-Propenethioic acid, 3,3-bis(methylthio)-S-methyl ester 60
was obtained by the debenzylation of S-methyl 2-benzoyl-
3,3-bis(methylsulfanyl)-2-propenioate 59 (2.9 g, 10
mmol) as yellow oil. Yield 1.6 g (85%). IR νmax/cm−1 1627,
1485, 1075. 1H NMR (300 MHz, CDCl3) δ 2.34 (s, 3H,
SCH3), 2.43 (s, 3H, SCH3), 2.48 (s, 3H, SCH3), 5.93 (s,
1H, CH) ppm. 13C NMR (75.47 MHz, CDCl3) δ 11.47,
14.70, 16.87 (SCH3), 111.78 (vinyllic), 157.76 (thiolester
carbonyl), 184.47 (vinyllic).

6.4.9 General Procedure for the synthesis of 6-Anilino-5-benzoyl-1,3-dibenzyl-
2,4(1H,3H)-pyrimidinedione 62

α-oxoketene N,S-acetal 53a was dissolved in dichloromethane (15 mL)
followed by dibenzyl urea (10 mmol). To the reaction mixture silver trifluoroacetate
was added and stirred for 10 minutes. The voluminous precipitate formed was
allowed to settle and the solvent was decanted. The precipitate was again washed with
dichloromethane (20 mL) and decanted. The combined solvents were evaporated and
the residue was filtered through a short silica gel column using hexane ethylacetate
(3:1) to afford 62.

6-Anilino-5-benzoyl-1,3-dibenzyl-2,4(1H,3H)-pyrimidinedione 62 was obtained by the reaction of 1-
benzenepropanethioic acid, α-[Z]-(methylthio)
(phenylamino)methylidene]-β-oxo-,S-methyl ester 51a
(3.3 g, 10 mmol) with N,N'-dibenzyl urea 61 2.4 g (10
mmol) in presence of silver trifluoroacetate (20 mmol) in
dichloromethane as a pale yellow glass. Yield 3.3 g (64%).
IR $v_{\text{max}}$/cm$^{-1}$ 1720, 1661 and 1566. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.12 ppm (s, 4H, PhCH$_2$), $\delta$ 7.10-7.67 (m, 20 H, aromatic), $\delta$ 9.30 (bs, 1H, NH) ppm. $^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta$ 45.84 (CH$_2$), $\delta$ 120.57, 120.72, 129.00, 129.97, 134.79, 136.43, 137.93 (aromatic), 164.07 and 196.95 (carbonyl) ppm. EIMS m/z (%) 487 ($M^+$ (12), 395 (23), 366 (18), 254 (28), 239 (67) and 105 (100).

References


For a review of pyrrole synthesis using vinylogous iminium salt derivatives, see Chapter 2, PP; 24. 25.


