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The Application of Vinylogous Iminium Salt Derivatives to a Regiocontrolled and Efficient Relay Synthesis of Lukianol A and Related Marine Natural Products[1]

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Abstract: Numerous novel pyrrole containing marine natural products have been shown to possess interesting biological properties. These compounds have been the synthetic targets of several research groups and we have previously reported synthetic methods which utilize vinylogous iminium salt derivatives as building blocks for analogous pyrrole systems. We now report a novel and regiocontrolled synthesis of a known pyrrole synthetic precursor to the compounds Lukianol A and Lammelarin O dimethyl ether based on this synthetic methodology.

Key Words: pyrroles; iminium salts; enals; natural products.

Numerous marine natural products[2] containing a pyrrole nucleus have received significant recent attention as a result of their cytotoxic activity[3] against a variety of cancer cell lines. These molecules exhibit cytotoxic effects against multidrug-resistant cell lines and have the ability to reverse this resistance when used in concert with other standard chemotherapeutic agents. Two of these active, natural products, Lamellarin O (**1**) and Lukianol A (**2**), have been the targets of successful synthetic efforts by a number of research groups. Boger and coworkers[4] have reported the most recent contribution to this class of targets, and their strategy involves the conversion of an appropriately substituted 1,2-diazine to the key pyrrole intermediate (**3**) by reduction with zinc and acetic acid. The requisite 1,2-diazine is constructed by a Diels-Alder reaction between an alkyne and a heteroaromatic tetrazine. Furstner and coworkers[5] have used a quite different strategy which employs the formation of an appropriately substituted vinylogous amide which is subsequently acylated and then undergoes a titanium-induced ring closure to give the key pyrrole synthon (**4**). Banwell and Hockless[6] have also prepared

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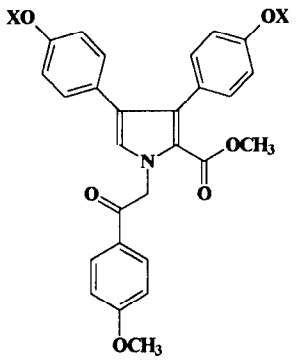
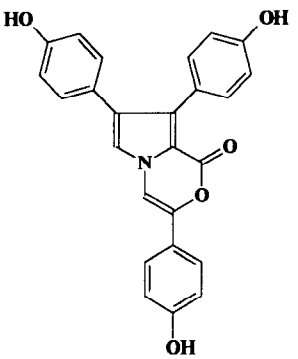
the Furstner synthon (**4**) by first preparing 2-carbomethoxy-3,4-dibromopyrrole and carrying out a Stille type cross-coupling reaction with the appropriately substituted aryl stannane. However, the common theme in all three synthetic approaches involves the regiocontrolled synthesis of a key tri- or tetrasubstituted pyrrole, which is then converted to the desired natural product.

Figure 1

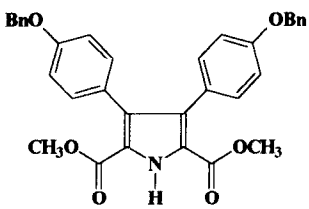


Lamellarin O (1a), X = H

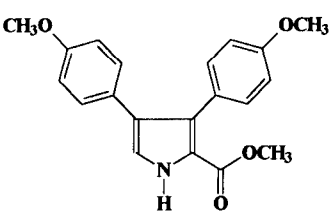
Lamellarin O dimethyl ether (1b), X = CH_3



Lukianol A (2)



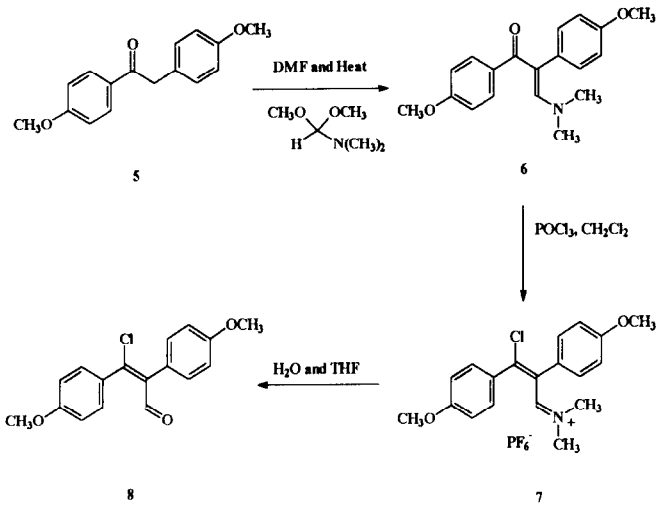
Boger intermediate (3)



Furstner intermediate (4)

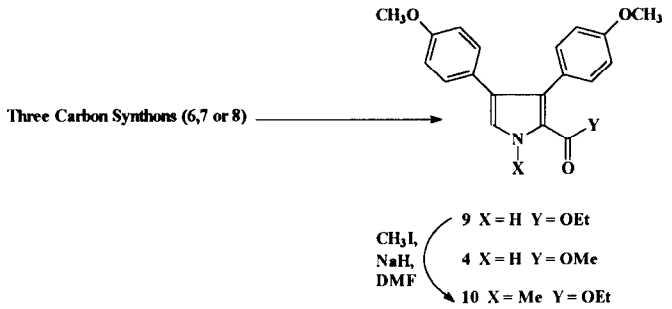
Recently we have reported[7] the regiocontrolled synthesis of a variety of 2,3,4-trisubstituted pyrroles which employs the condensation of amino acid esters with vinylogous iminium salt derivatives. The vinylogous iminium salt derivatives that we examined as possible 3-carbon synthons were vinylogous amides, chloropropeniminium salts and β-chloroenals. We now report an efficient, complementary, three-step synthesis for the Furstner intermediate[5] (**4**), which thereby demonstrates a relay synthesis of Lamellarin O dimethyl ether (**1b**) and Lukianol A (**2**) by this methodology (Scheme 1 and Table 1).

Scheme 1



The vinylogous amide (**6**) is prepared from the commercially available α-arylacetophenone (**5**) in 91% yield using DMF acetal. This material is then converted to the chloropropeniminum salt by reaction with phosphorus oxychloride, and the salt (7) is precipitated in 73% yield with sodium hexafluorophosphate. The crude salt (unprecipitated and without purification) is subsequently hydrolyzed in a water/THF mixture to give the β-chloroenal (**8**) as a mixture of E and Z isomers in 95% yield (based on the vinylogous amide). The overall yield for the two step process is 86%. The 80:20 ratio of E:Z isomers is easily observed based on the chemical shifts of the aldehyde protons (9.64 ppm E isomer and 10.60 ppm Z isomer) as pointed out by Lloyd[8] and coworkers. However, the isomeric mixture of β-chloroenals can be used as is for subsequent conversion to the key pyrrole synthon (**4**). At this point we decided to carefully consider all three synthons (**6**, **7** and **8**) as possible intermediates for the synthesis of the Furstner pyrrole[5] (**4**). We examined the condensation of these substrates with glycine methyl ester, glycine ethyl ester and N-methylglycine ethyl ester under acidic (HOAc), neutral (DMF) and basic conditions (NaH, DMF) and these results are reported in Table 1. Analysis of the results reported in Table 1 suggest that reaction of a glycine ester or it's N-methyl analog with the β-chloroenal (**8**) under neutral conditions gives the best yields (82-92% range) of the respective 2,3,4-trisubtitued pyrroles. It should also be emphasized that the isomeric mixture of β-chloroenals was used in all such condensation reactions and no unreacted β-chloroenal could be detected by ^{1}H NMR when the crude reaction product was analyzed. This suggests that both isomers potentially lead to the formation of the desired pyrrole. Glycine esters and N-methyl glycine ethyl ester were examined since previous studies[9] by our research group had indicated that the N-unsubstituted amino acid esters could behave differently from their N-substituted counterparts.

Table 1. Reactions of Various 3-Carbon Synthons with Glycine Derivatives Under Acidic, Neutral and Basic Conditions



			% Yield[a]		
Amino Acid Ester	**Substrate**	**Product**	**HOAc**	**DMF**	**NaH/ DMF**
Glycine[b]	6	4	NPD	NPD	NPD
Glycine[b]	7	4	NPD	NPD	77
Glycine[c]	7	9	-----	-----	53
Glycine[b]	8	4	NPD	82	NPD
N-Methylglycine[c]	6	10	68	NPD	NPD
N-Methylglycine[c]	7	10	49	26	43
N-Methylglycine[c]	8	10	NPD	92	NPD

[a]All yields represent isolated and analytically pure products and NPD = no pyrrole product detected.

[b]Represents the use of a methyl ester hydrochloride.

[c]Represents the use of an ethyl ester hydrochloride.

An example of such behavior can be seen in Table 1 where the vinylogous amide (**6**) reacts with N-methyl glycine ethyl ester under acidic conditions to produce the corresponding pyrrole (**10**). In contrast, glycine methyl ester did not react successfully under analogous conditions. Additionally, the chloropropeninimium salt (**7**) reacts with N-methyl glycine ethyl ester successfully under all three sets of conditions (acidic, neutral and basic), whereas glycine methyl ester only reacts successfully under basic conditions. Interestingly, in the case of the β-chloroenal (**8**), both N-substituted and N-unsubstituted glycine esters react successfully under neutral conditions. From a mechanistic standpoint when considering the chloropropeniminium salt (**7**) and the β-chloroenal (**8**), the amino group of the amino acid ester presumably exchanges with the iminium or carbonyl oxygen respectively, to give an intermediate which is capable of forming an azomethine ylid or an azapentadienyl system. Such species should then undergo cyclization and dehydrohalogenation to give the respective pyrroles. When the vinylogous amide (**6**) is used in the condensation reaction, the amino group of the amino acid ester is thought to undergo an exchange reaction with the amine of the vinylogous amide followed by cyclodehydration to the respective pyrrole[7].

In order to unequivocally establish the regiochemical relationship between the pyrroles (**4, 9** and **10**), compound **9** was treated with iodomethane, sodium hydride and DMF in which case compound **10** was

produced in 97% yield based on NMR and TLC comparisons with an authentic sample prepared via the N-methyl glycine ethyl ester route. The successful reaction of the β-chloroenal (**8**) with methyl glycinate hydrochloride in DMF (82% yield, Table 1) produced the Furstner pyrrole[5] (**4**), thereby constituting a relay synthesis of Lamellarin O dimethyl ether (**1b**) and Lukianol A (**2**). The overall yield for the three-step process, which utilizes the β-chloroenal (**8**) as a mixture of isomers (produced directly from the vinylogous amide), is 71% and is very competitive with the other reported methods. Our material (**4**) proved to be analytically pure and was identical by ^{1}H NMR and ^{13}C NMR to that of Furstner.

In summary, we have demonstrated that the vinylogous amide (**6**), the chloropropeniminium salt (**7**) and the β-chloroenal (**8**) react successfully with glycine esters in a regiocontrolled and efficient fashion to produce 2,3,4-trisubstituted pyrroles (**4**, **9**, **10**) in good yield. These substances have been shown to be valuable intermediates for the preparation of several pyrrole-containing marine natural products, which exhibit interesting and useful pharmacological properties. Work is currently underway to extend this methodolgy to related biologically interesting marine natural products.

Experimental Section

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific). NMR spectra were obtained on a 200 MHz spectrometer in either $CDCl_3$ or d_6-DMSO solutions. IR spectra were obtained as either nujol mulls or KBr pellets. High resolution mass spectra were supplied by Dr. Ronald G. Smith of the Monsanto Analytical Sciences Center. All samples gave ^{1}H and ^{13}C NMR spectra consistent with a sample purity in excess of 95%. Melting points and boiling points are uncorrected. Radial chromatographic separations were carried out on a Chromatotron using silica gel plates of 1-mm or 2-mm thickness with a fluorescent backing or by standard chromatographic techniques.

Preparation of 3-Dimethylamino-1,2-bis(4-methoxyphenyl)propenone (6). To a solution of desoxyanisoin (**5**) (5.00g, 19.5 mmol) in 100 mL of DMF was added 10.4 mL (9.30g, 78.0 mmol) of N,N-dimethylformamide dimethyl acetal. The solution was stirred under a nitrogen atmosphere at reflux for 18 h. The solvent was removed by Kugelrohr distillation at reduced pressure to yield a brown solid (5.00g, 91% yield) which was of sufficient purity for use in subsequent reactions. An analytical sample was prepared by radial chromatography using 80:20, hexane:EtOAc as the eluant: mp 114-117 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.73 (s, 6H), 3.78 (s, 6H), 6.73-6.82 (m, 4H), 7.05 (d, J = 9 Hz, 2H), 7.34 (s, 1H), 7.42 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 43.9, 55.3, 111.6, 113.0, 113.4, 113.8, 130.2, 131.2, 133.2, 134.5, 153.3, 158.3, 160.8 and 194.3; HRMS: calcd. for $C_{19}H_{21}NO_3$ ($M+H^+$) 312.1600, found 312.1599.

Preparation of N,N-Dimethyl-2,3-bis(4-methoxyphenyl)-3-chloropropeniminium salt (7). To a solution of 1.50 g (4.82 mmol) of vinylogous amide (**6**) in 35 mL of CH_2Cl_2 was added 1.51 g (9.88 mmol) of phosphorous oxychloride. The resulting mixture was refluxed for 5 hrs and the solvent was removed in vacuo. To the residue was added a cold solution of 1.62 g (9.64 mmol) of sodium hexafluorophosphate in 30 mL of

methanol and the mixture was allowed to stand in a freezer overnight. The resulting yellow crystals (1.68 g, 73.4 % yield) exhibited the following properties: mp 166-168 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.99 (s, 3H), 3.65 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 7.03 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 7.63 (d, J = 8 Hz, 2H) and 7.88 (s, 1H); ^{13}C NMR (CD_3COCD_3) δ 44.8, 51.3, 55.9, 56.4, 115.7, 115.9, 127.9, 129.7, 130.3, 132.6, 134.4, 158.7, 161.7, 165.2 and 170.4; HRMS: calcd. for $C_{19}H_{21}NO_2Cl$ ($M+H^+$) 330.1261, found 330.1267.

Preparation of 3-Chloro-2,3-bis(4-methoxyphenyl)propenal (8). To a solution of 1.50 g (4.82 mmol) of vinylogous amide (**6**) in 35 mL of CH_2Cl_2 was added 1.51 g (9.88 mmol) of phosphorous oxychloride. The resulting mixture was refluxed for 5 hrs and the solvent was removed in vacuo. To the residue was added 100 mL of a 50:50 mixture of THF:water and the resulting mixture was stirred overnight at 25°C. The THF was removed in vacuo and the residue was extracted with chloroform (3 x 50 mL). The combined chloroform extract was dried ($MgSO_4$), filtered and concentrated in vacuo to yield a yellow solid (1.38 g, 95 % yield). This material could be used without further purification but an analytical sample was prepared by radial chromatography on a 2 mm thick plate of silica gel using an 80:20 mixture of hexane:EtOAc. The resulting purified material had a mp of 132-134 °C and consisted of a mixture of E (major) and Z (minor) isomers. The E isomer exhibited the following properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.88 (s, 3H), 6.97 (d, J = 9 Hz, 4H), 7.24 (d, J = 9 Hz, 2H), 7.51 (d, J = 9 Hz, 2H) and 9.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.4, 55.7, 126.6, 128.3, 131.5, 131.9, 132.1, 132.4, 139.8, 155.3, 159.7, 162.2 and 190.7; IR (nujol) 1675 cm^{-1}; HRMS: calcd. for $C_{17}H_{15}O_3Cl$ ($M+H^+$) 303.0788, found 303.0782.

Preparation of Ethyl N-Methyl-3,4-bis(4-methoxyphenyl)-pyrrole-2-carboxylate (10) From a β-Chloroenal (8) Under Neutral Conditions. To a solution of 3-chloro-2,3-bis(4-methoxyphenyl)propenal (8) (195 mg, 0.64 mmol, a mixture of isomers) in 10 mL of dry DMF, was added ethyl N-methyl glycinate hydrochloride (139 mg, 0.64 mmol). The resulting mixture was stirred under an inert atmosphere at reflux for 20 hrs and the solvent was removed in vacuo via Kugelrohr distillation. The resulting dark residue was purified by dissolving it in EtOAc (50 mL) and passing the solution through a short plug of silica gel. After washing the plug with additional EtOAc (50 mL), the combined EtOAc fractions were concentrated in vacuo to yield a yellow-green oil (200 mg, 92% yield): bp 110-120°C at 2.0 torr; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (t, J = 7 Hz, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 4.08 (q, J = 7 Hz, 2H), 6.73 (d, J = 9 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 6.88 (s, 1H), 7.00 (d, J = 9 Hz, 2H) and 7.13 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 37.7, 55.2, 59.8, 113.1, 113.7, 120.7, 124.0, 126.7, 127.3, 128.5, 129.4, 131.1, 132.0, 158.0, 158.5 and 162.1; IR (nujol) 1690 cm^{-1}; HRMS: calcd. for $C_{22}H_{23}NO_4$ ($M+H^+$) 366.1705, found 366.1675.

Preparation of Ethyl 3,4-Bis(4-methoxyphenyl)pyrrole-2-carboxylate (10) From a Chloropropeniminium Salt (8) Under Basic Conditions. Into a round bottomed flask equipped with a condensor and magnetic stirrer and under a nitrogen atmosphere was placed 130 mg (3.28 mmol) of a 60%

mineral oil dispersion of sodium hydride. The dispersion was washed with a small amount of hexane which was removed via cannula and dry DMF (20 mL) was added. Glycine ethyl ester hydrochloride (214 mg, 1.54 mmol) was added followed by the addition of the chloropropeniminium salt (**8**) (304 mg, 0.64 mmol). The resulting mixture was stirred at 25°C for 1 hr and heated at reflux for an additional 21 hrs. The reaction mixture was cooled to 25°C, quenched with 30 mL of methanol and the solvents were removed in vacuo. The residue was dissolved in 20 mL of EtOAc and filtered through a short plug of silica gel. The silica gel plug was washed with additional EtOAc (60 mL) and the solvent was removed in vacuo to yield a brown solid (120 mg, 53% yield). An analytical sample was prepared by subjecting this material to radial chromatography using a 1 mm thick plate of silica gel and eluting with a 90:10 mixture of hexane:EtOAc which produced 90 mg (40% yield) of an off white solid: mp 119-123°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, J = 7 Hz, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 4.20 (q, J = 7 Hz, 2H), 6.75 (d, J = 8 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 7.00-7.06 (m, 3H), 7.20 (d, J = 8 Hz, 2H) and 9.30 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 55.3, 60.3, 113.2, 113.9, 120.0, 120.1, 126.6, 126.8, 127.4, 129.1, 129.7, 132.2, 158.3, 158.8 and 161.4; IR (KBr) 3300 and 1675 cm^{-1}; HRMS: calcd. for $C_{21}H_{21}NO_4$ (M+) 351.1471, found 351.1443.

Preparation of Ethyl N-Methyl-3,4-bis(4-methoxyphenyl)-pyrrole-2-carboxylate (10) by N-Methylation of the Corresponding Pyrrole. Into a round bottomed flask equipped with a condensor and magnetic stirrer and under a nitrogen atmosphere was placed 5 mg (0.2 mmol) of a 60% mineral oil dispersion of NaH. To the flask was then added 5 mL of dry DMF followed by ethyl N-methyl-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (**9**) (17 mg, 0.048 mmol). The resulting mixture was stirred for 30 mins and iodomethane (0.02 mL, 0.29 mmol) was added via syringe. After stirring for 23 hrs at 25°C, the reaction mixture was quenched with methanol (2 mL) and the solvents were removed in vacuo. The residue was partitioned between water (15 mL) and chloroform (3x15 ml) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil (17 mg, 97% yield) which was identical by ^{1}H NMR and TLC analysis to ethyl N-methyl-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (**10**) prepared directly from ethyl N-methyl glycinate hydrochloride and the β-chloroenal (**8**).

Preparation of Ethyl N-Methyl-3,4-bis(4-methoxyphenyl)-pyrrole-2-carboxylate (10) From a Vinylogous Amide (6) Under Acidic Conditions. Into a round bottomed flask was placed 10 mL of glacial HOAc, 3-dimethylamino-1,2-bis(4-methoxyphenyl)propenone (**6**) (200 mg, .640 mmol) and N-methyl glycine ethyl ester hydrochloride (238 mg, 1.54 mmol). The resulting mixture was refluxed overnight, cooled to 25°C and diluted with 100 mL of CH_2Cl_2. The mixture was then carefully extracted with saturated, aqueous sodium bicarbonate until evolution of carbon dioxide ceased. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to yield an oil. This oil was dissolved in 50 mL of EtOAc and filtered through a short plug of silica gel. The filtrate was concentrated in vacuo and the residue was subjected to radial chromatography on a 2 mm thick plate of silica gel with 80:20 hexane:EtOAc. Concentration in vacuo of the fractions containing the major component produced 160 mg (68% yield) of an oil which exhibited ^{1}H NMR and TLC behavior

identical to ethyl N-methyl-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (**10**) prepared from the β-chloroenal (**8**) under neutral conditions.

Preparation of Methyl 3,4-Bis(4-methoxyphenyl)pyrrole-2-carboxylate (Furstner intermediate, 4). To a solution of 3-chloro-2,3-bis(4-methoxyphenyl)propenal (8) (79 mg, 0.26 mmol), which was used as a mixture of isomers and was prepared directly from vinylogous amide (**6**), in 10 mL of dry DMF was added methyl glycinate hydrochloride (54 mg, 0.43 mmol). The solution was stirred under an inert atmosphere at reflux for 20 hrs and the solvent was removed in vacuo via Kugelrohr distillation. A crude dark residue was obtained which was purified by dissolving it in EtOAc (50 mL) and passing the solution through a short plug of silica gel. After washing the plug with additional EtOAc (~50 mL), the combined EtOAc fractions were concentrated in vacuo to yield a light brown solid (72 mg, 82% yield): mp of 168-171°C (lit.[5] 169-171°C) and gave ^{1}H NMR, ^{13}C NMR and MS spectra identical to that reported by Furstner and coworkers[5].

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