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An efficient 1,2,4-triazine-based route to the louisianin alkaloids

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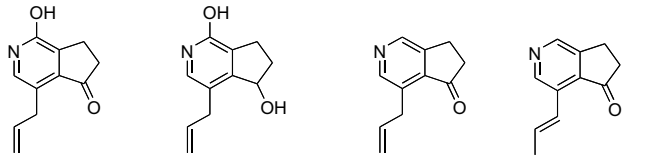
Abstract

A new, short and efficient route to louisianins C and D is described in which the pyridine ring is constructed from a disubstituted 1,2,4-triazine by an inverse-electron-demand Diels–Alder/retro-Diels–Alder/aromatisation cascade sequence. This eight-step route produces louisianin C in 16% overall yield from the commercially available 5-chloropent-1-yne.

Louisianins A–D (**1**–**4**) are a family of alkaloids reported in 1995, which were isolated from a *Streptomyces* sp. obtained from a soil sample collected in Louisiana (USA).[1] Louisianin A proved to be a potent inhibitor of testosterone-responsive carcinoma SC115, while louisianins C and D were potent suppressors of cultured vascular endothelial cells in vitro (Fig. 1).[2,3]

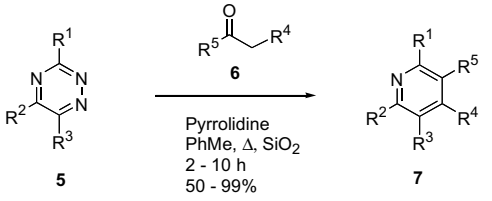
The chemical interconversion of louisianins has been described,[3] but it was not until 2003 that Kelly's group published the first total synthesis of louisianin C **3**.[4] This was achieved in 9 steps (11% overall yield) starting from 3,5-dibromopyridine; the key cyclopentane-forming step utilised an intramolecular, fluoride-induced silylpyridine to aldehyde cyclisation. Then, in 2006, Chang et al. reported the first total synthesis of louisianin A **1** in 7 steps (24% overall yield) starting from 2-chloro-4-cyanopyridine.[5] In this route, the cyclopentane construction was achieved using a Dieckmann–Thorpe cyclisation. Both the routes mentioned started from the commercially available pyridine derivatives, and the substituents were introduced in a stepwise manner performing the annulation at a late stage of the synthesis. Recently, however, Chen et al. prepared louisianin D starting from ethyl cyclopentene-1-carboxylate and using a [3+3] annulation strategy to construct the heterocyclic ring.[6] The complete route involved 10 steps (20% overall yield).



Louisianin A (**1**) Louisianin B (**2**) Louisianin C (**3**) Louisianin D (**4**)

Fig. 1. The louisianin alkaloids.

We have recently reported several triazine-based routes to highly substituted pyridines.[7] The most straightforward procedure (Scheme 1) involves the in situ enamine generation from ketone **6** and pyrrolidine using Boger's procedure[8] followed by a tandem inverse-electron-demand Diels–Alder/retro-Diels–Alder sequence; the resulting dihydropyridine then undergoes in situ aromatisation to give pyridine **7** expedited by the presence of silica gel.[9]



Scheme 1.

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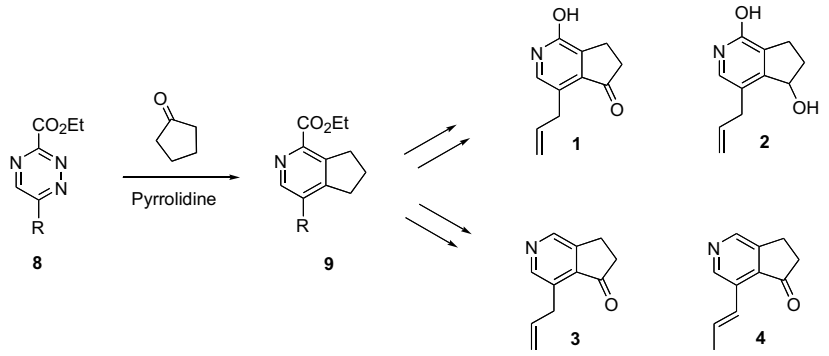


Scheme 2.

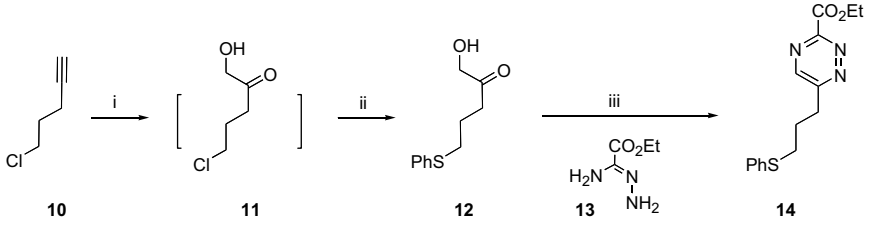
The louisianin alkaloids, with their pyridine-based core and promising anti-androgenic properties, represent attractive targets to validate this triazine methodology. We therefore designed the unified route to the louisianins shown in Scheme 2; the ester group was included at position 3 of the triazine ring in order to enhance its reactivity in the inverse-electron-demand Diels–Alder reaction and also to provide a 'handle' to ensure the regioselectivity of the subsequent pyridone formation.

The recent publications in this area[4–6] prompt us to present a preliminary report describing a triazine-based synthesis of louisianin C **3**, together with its isomerisation to louisianin D **4**.

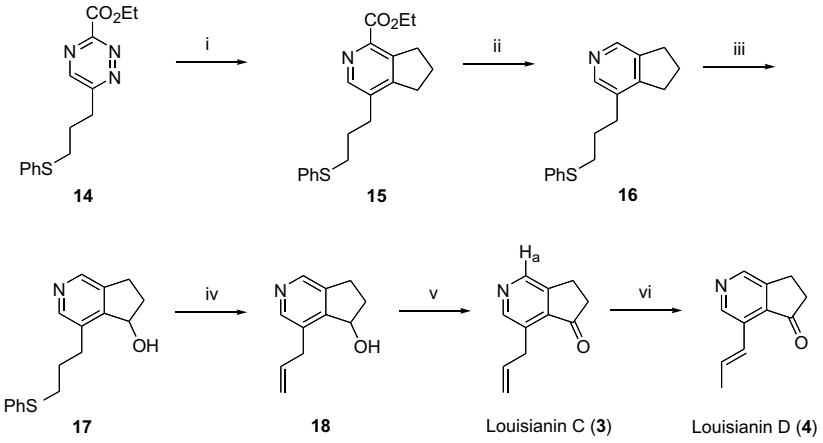
3-Ethoxycarbonyl-5-(3′-phenylthiopropyl)-1,2,4-triazine **14** was chosen as the starting material in order to have a masked propenyl unit at position 6.[10] This novel triazine was prepared by the route shown in Scheme 3. Thus, the commercially available 5-chloropent-1-yne **10** was oxidised using phenyliodine(III) bis(trifluoroacetate) (PIFA)[11] to produce α-hydroxy ketone **11**. Without purification, ketone **11** was treated with potassium thiophenolate, prepared in situ, to give sulfide **12** in 60% isolated yield after column chromatography over the two steps. Next, utilising our recently described procedure for preparing 3,6-disubstituted triazines,[7c] α-hydroxy ketone **12** was first condensed with the ethyl oxalamidrazonate **13**[12] and the product oxidised with MnO_2 producing triazine **14** in 75% overall yield.[13]

Having the key triazine **14** in hand, we were in a position to investigate the crucial Diels–Alder cascade, producing the required annulated pyridine **15** containing the complete carbon skeleton of the louisianin alkaloids (Scheme 4). Thus, the thermolysis of triazine **14** with cyclopentanone and pyrrolidine followed by silica-mediated aromatisation gave pyridine **15** in a gratifying 89% yield.[14,15] The decarboxyethylation of the pyridine ester **15** proved impossible using standard conditions.[16] Success was achieved, however, by the treatment of pyridine ester **15** with very dilute aqueous hydrochloric acid in a microwave reactor (CEM Discover®) giving pyridine **16** in 85% yield after a basic work-up. To the best of our knowledge, this is the first example of the direct decarboxyalkylation of a pyridine ester using microwave acceleration.

Next, regioselective cyclopentane hydroxylation was required in order to prepare alcohol **17**. We first investigated the LiHMDS/O_2 procedure developed by Chen et al.[6] Unfortunately, on substrate **16**, this procedure gave a mixture of two inseparable compounds (2:1 ratio, NMR) and recovered starting material. Eventually, using an observation made by Corey and Ensley,[17] we found that the addition of triethylphosphite to the benzylic anion generated using LiHMDS under kinetic conditions, and then oxidation gave the required alcohol **17** as the only product in 79% yield. At this stage, the alkene was revealed by chemoselective sulfide oxidation (*m*-CPBA in CH_2Cl_2 at −78 °C) followed by thermolysis in xylene, in the presence of $CaCO_3$. The resulting alkene **18** (76% yield from **17**) was obtained without contamination by the isomerised conjugated alkene. The final step in order to obtain louisianin C **3** involved the oxidation of the benzylic alcohol but this proved to be surprisingly difficult. Several standard oxidants (including CrO_3[3]) gave only low to moderate yields of the ketone; however, PCC supported on basic alumina gave the desired louisianin C **3** in 80% yield. Louisianin



Scheme 3. Reagents and conditions: (i) PIFA (1.2 equiv), $CH_2Cl_2/CH_3CN/H_2O$ (8:2:1), 50 °C, 5 h, then satd aq $NaHCO_3$, rt, 2 h; (ii) PhSH (1.1 equiv), KOH (1.1 equiv), H_2O/THF (50:1), 80 °C; 2 h, 60% from **10**; (iii) THF, 80 °C, 4 h, then MnO_2 (5 equiv), toluene, 120 °C, 18 h, 75%.



Scheme 4. Reagents and conditions: (i) cyclopentanone (1.2 equiv), pyrrolidine (1.2 equiv), xylene, 160 °C, 10 h, then silica, 18 h, 89%; (ii) concd HCl/H_2O (1:50), 185 °C, MW, 1 h then aq K_2CO_3, 85%; (iii) (a) LiHMDS (10 equiv), THF, −5 °C, 45 min; (b) $P(OEt)_3$ (2.2 equiv), 15 min; (c) O_2, 8 h, 79%; (iv) (a) *m*-CPBA (1.2 equiv), CH_2Cl_2, −78 °C, 1 h; (b) $CaCO_3$ (5 equiv), xylene, 160 °C, 18 h, 76%; (v) PCC supported on basic alumina (2 equiv), CH_2Cl_2, rt, 3 h, 80%; (vi) MTBD (1.2 equiv), toluene, 80 °C, 6 h, 78%.

C (**3**) was fully characterised[18] and gave consistent data to those published [e.g., δ_C ($CDCl_3$) 208.0 (C=O); δ_H ($CDCl_3$) 8.76 (1H, s, H_a); lit.[2] δ_C ($CDCl_3$) 207.3 (C=O); δ_H ($CDCl_3$) 8.75 (1H, s, H_a)]. Treatment of louisianin C in toluene in the presence of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) gave clean alkene isomerisation producing louisianin D (**4**) in 78% isolated yield.[3,19] The authenticity of louisianin D (**4**) was confirmed spectroscopically[20] and by comparison with the published data (mp 83–85 °C; lit.[3] mp 83–86 °C).

In summary, a new route to louisianins C and D has been developed in which the pyridine ring is constructed from a disubstituted 1,2,4-triazine by an inverse-electron-demand Diels–Alder/retro-Diels–Alder/aromatisation cascade sequence. This route is short, efficient (only 5 steps and 37% overall yield of louisianin C from triazine **14**) and ideal for analogue synthesis. We are currently preparing novel louisianin analogues and extending this route to prepare the other members of the louisianin family.

Acknowledgements

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13. A solution of 1-hydroxy-5-(phenylthio)pentan-2-one **12** (1.47 g, 7.00 mmol) and ethyl oxalamidrazonate **13** (1.10 g, 8.40 mmol) in anhydrous THF (30 mL) was stirred at 80 °C for 4 h, then cooled down and concentrated to half volume. The yellow solution thus obtained was diluted with toluene (70 mL), MnO_2 (3.04 g, 35.00 mmol) was added and the mixture was heated up to 120 °C for 18 h. The reaction mixture was then cooled down to ca. 60 °C, and filtered through a pad of Celite, which was washed with EtOAc–MeOH (2:1). The combined organic fractions were concentrated in vacuo and the residue was purified by silica gel chromatography (petroleum ether–ethyl acetate, 2:3) to give ethyl 6-(3-(phenylthio)propyl)-1,2,4-triazine-3-carboxylate **14** (1.59 g, 75%) as a yellow oil, ^1H NMR (400 MHz, $CDCl_3$) 8.64 (1H, s), 7.37–7.26 (4H, m), 7.24–7.18 (1H, m), 4.59 (2H, q, *J* 7.2 Hz), 3.25 (2H, t, *J* 7.6 Hz), 3.04 (2H, t, *J* 7.0 Hz), 2.21 (2H, tt, *J* 7.6, 7.0 Hz), 1.49 (3H, t, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 162.9, 162.7, 155.8, 149.8, 135.6, 129.9, 129.2, 126.6, 63.0, 32.7, 31.8, 27.3, 13.7; IR ν_{max}(film)/cm^{-1} 3059, 2982, 2935, 1745, 1619, 1584, 1481, 1440, 1311, 1234, 1180; MS (ESI, *m*/*z*): 304 (MH^+, 100%), 326 (MNa^+, 54); HMRS (ESI): found: 326.0930; $C_{15}H_{17}N_3O_2SNa$ requires: 326.0934 (1.09 ppm error).

14. A solution of triazine **14** (2.00 g, 6.59 mmol), pyrrolidine (660 μL, 7.91 mmol) and cyclopentanone (700 μL, 7.91 mmol) in xylene (32 mL) was heated at 160 °C in a sealed tube (Ace pressure tube) for 10 h. The reaction mixture was cooled to rt, silica (2.00 g, Fluka, flash chromatography Silica Gel 60, 220–440 mesh) was added and the yellow suspension obtained heated to reflux for an additional 18 h. The mixture was then cooled to rt, filtered through a Celite pad, concentrated and the residue obtained was purified by silica gel chromatography (petroleum ether–ethyl acetate, 1:1) to give pyridine **15** (2.00 g, 89%) as a pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) 8.34 (1H, s), 7.36–7.25 (4H, m), 7.23–7.17 (1H, m), 4.46 (2H, q, *J* 7.2 Hz), 3.33 (2H, t, *J* 7.6 Hz), 2.94 (2H, t, *J* 7.0 Hz), 2.87 (2H, t, *J* 7.7 Hz), 2.80 (2H, t, *J* 7.6 Hz), 2.10 (2H, tt, *J* 7.7, 7,6 Hz), 1.97–1.87 (2H, m), 1.44 (3H, t, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 166.3, 154.8, 147.9, 143.4, 142.0, 136.5, 136.1, 129.7, 129.2, 126.4, 61.2, 32.9, 32.6, 30.5, 29.5, 28.4, 23.9, 14.0; IR ν_{max}(film)/cm^{-1} 3056, 2977, 2955, 1729, 1714, 1618, 1583, 1480, 1438, 1298, 1231, 1176; MS (ESI, *m*/*z*): 342 (MH^+, 100%), 364 (MNa^+, 14); HMRS (ESI): found: 342.1518; $C_{20}H_{24}NO_2S$ requires: 342.1522 (1.26 ppm error).
15. Pyridine **14** can also be prepared using our microwave procedure[7b] in comparable yields. On a small scale (250 mg), the MW procedure is preferred in view of the short reaction time (1 h). However, the silica-procedure is favoured for larger scale reactions.
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18. Louisianin C (**3**): pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) 8.76 (1H, s), 8.47 (1H, s), 5.98 (1H, ddt, *J* 16.2, 9.6, 6.6 Hz), 5.11–5.04 (2H, m), 3.80 (2H, d, *J* 6.6 Hz), 3.16 (2H, dd, *J* 5.9, 6.0 Hz), 2.74–2.67 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 208.0, 149.4, 148.5, 148.2, 140.0, 135.7, 133.3, 117.0, 36.3, 32.4, 22.9; IR ν_{max}(film)/cm^{-1} 3078, 2978, 2925, 1716, 1637, 1586, 1463, 1418, 1285, 1189, 1048, 917; MS (ESI, *m*/*z*): 174 (MH^+); HMRS (ESI): found: 174.0913, calculated for $C_{11}H_{12}NO$: 174.2191 (1.32 ppm error).
19. Surprisingly, the use of polystyrene-bound 1,5,7-triazabicyclo[4.4.0]-dec-5-ene in toluene at reflux gave louisianin D (**4**) in only 10% yield.
20. Louisianin D (**4**): white solid, mp 83–85 °C (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) 8.78 (1H, s), 8.67 (1H, s), 7.40 (1H, dd, *J* 1.8, 16.0 Hz), 6.55 (1H, dq, *J* 6.8, 16.0 Hz), 3.13 (2H, dd, *J* 6.0, 5.9 Hz), 2.73–2.69 (2H, m), 1.98 (3H, dd, *J* 1.8, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 208.2, 147.9, 145.3, 145.2, 137.5, 132.6, 131.1, 123.9, 36.2, 22.72, 18.7; MS (ESI, *m*/*z*): 174 (MH^+); HMRS (ESI): found: 174.0913, calculated for $C_{11}H_{12}NO$: 174.2191 (2.28 ppm error).