A brief total synthesis of Pyrrolostatin

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A brief total synthesis of Pyrrolostatin

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Abstract- A novel total synthesis of the unusual naturally occurring 2,4-disubstituted pyrrole, Pyrrolostatin **1**, is described, which features formation of the central pyrrole ring by a recently developed silver(I)-catalysed 5-*endo*-dig cyclisation.

Keywords: Pyrrolostatin; synthesis; pyrroles; silver-catalysed; cyclisation.

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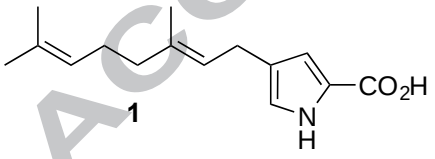
In contrast to the ubiquitous occurrence of tetrapyrroles in the form of haem and the chlorophylls and their metabolites in almost all life forms, there are many fewer examples of naturally occurring pyrroles that have come to light thus far. Probably the best known are the Prodigiosins (Prodiginines),[1,2] based on a pyrrolyl-dipyrromethane core, along with the unique Roseophilin in which the central pyrrole residue is replaced by a furan.[1] Monopyrroles are even rarer, thus far being represented by Pyrrolostatin **1**,[3] together with the highly oxidised 3-farnesyl pyrrole, Glaciapyrrole A[4] and four unprecedented derivatives of 4-farnesyl-2-nitropyrrole –Nitropyrrolin A[5] and the Heronapyrroles A-C.[6] Once again, the farnesyl side chain in these latter derivatives is also highly oxidised by *bis*-hydroxylation and subsequent *bis*-tetrahydrofuran formation. The latter biosynthetic idea has recently been beautifully illustrated in a polyene epoxide cascade synthetic sequence leading to Heronapyrrole C.[7] This contrasted with the somewhat dismal selectivities achieved in preparing suitable 4-substituted-2-nitropyrroles or 4-substituted pyrrole-2 carboxylates, which resulted in an entirely separate study in search of solutions to this problem.[8] In fact, 2,4-disubstituted pyrroles in general are a challenge to synthesise efficiently, a problem which clearly was encountered in Brimble and co-workers recent successful alternative synthesis of Heronapyrrole C.[9] The New Zealand group were fortunately able to define suitable *N*-protecting groups and conditions to facilitate efficient 4-iodination of 2-nitropyrrole derivatives.



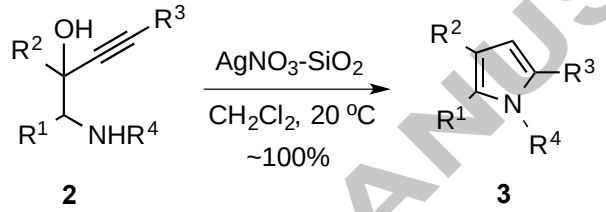
1

Figure 1. The structure of Pyrrolostatin **1**

Much the same is true of the only previously reported synthesis of pyrrolostatin **1** which, while being agreeably brief, suffers from a very poor 18% yield in the key pyrrole forming step using the Barton-Zard method.[10] Given that pyrrolostatin possesses lipid peroxidation inhibitory activity on a par with

Vitamin E, it is a worthwhile target, especially in view of its close relationship with the foregoing oxidized farnesylpyrrole derivatives.

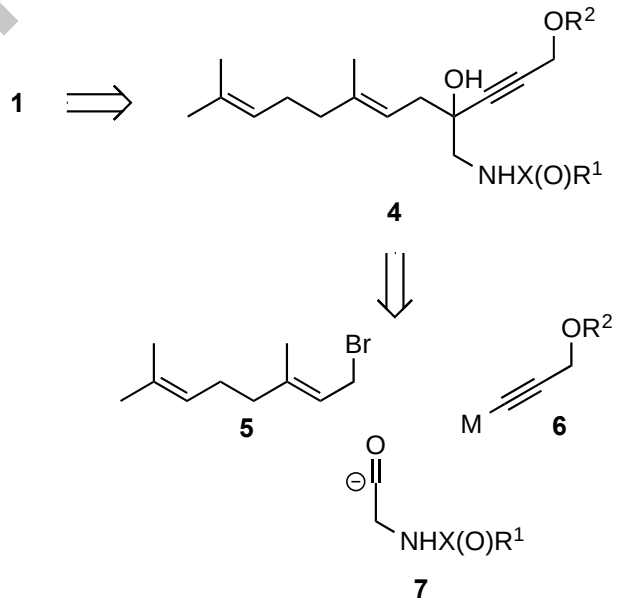
We have recently developed an extremely efficient and general approach to pyrroles **3**, including 2,4-disubstituted examples,[11] which features silver(I)-catalysed cyclisations of aminoalkynol derivatives **2** (Scheme 1). We therefore reasoned that it should be possible to use this methodology in a relatively brief synthesis of pyrrolostatin **1**, hopefully in good overall yield. Herein, we report on the successful outcome this idea.



2 **3**

Scheme 1. Pyrrole formation from amino alkynol derivatives using $AgNO_3$-SiO_2.

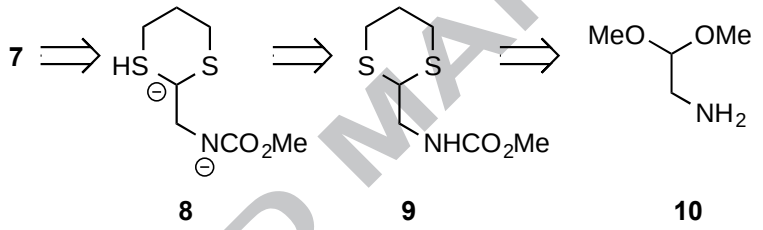
Given that a key step would be a cyclisation of the type outlined in Scheme 1, an obvious disconnection led back to aminoalkyne diol derivatives **4**.



Scheme 2. The basic retrosynthetic plan.

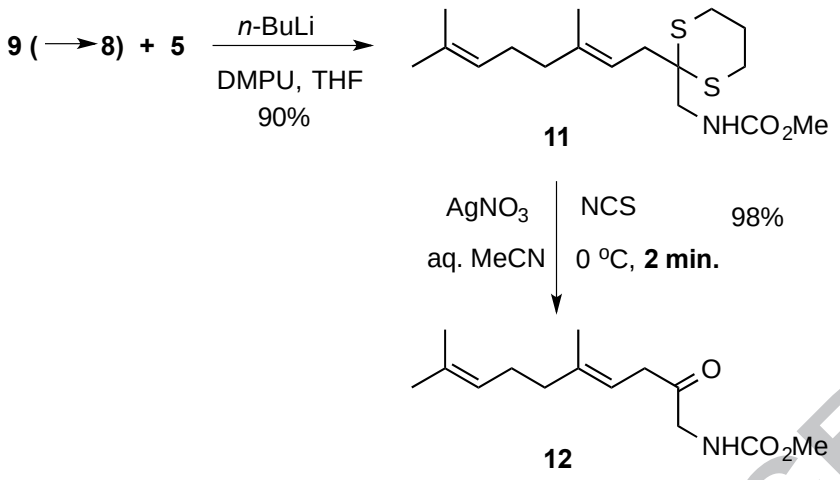
Two further disconnections then seemed clear: firstly the geranyl chain would be introduced as an electrophilic unit, most likely in the form of geranyl bromide **5**, which would be followed by addition of the alkyne unit as a nucleophile **6**. This reasonably obvious strategy, however, then left an odd-looking umpolung amino-ketone unit **7** (Scheme 2).

This naturally suggested a 1,3-dithiane intermediate; fortunately, such a species, in the form of dianion **8**, has been well studied by Seebach and colleagues.[12] Given the correct solvents and conditions, it can be readily formed from the corresponding neutral precursor **9** which, in turn, is prepared from commercially available aminoacetaldehyde dimethyl acetal **10** (Scheme 3).



Scheme 3. Steps leading to the amino-dithiane nucleophile **8.**

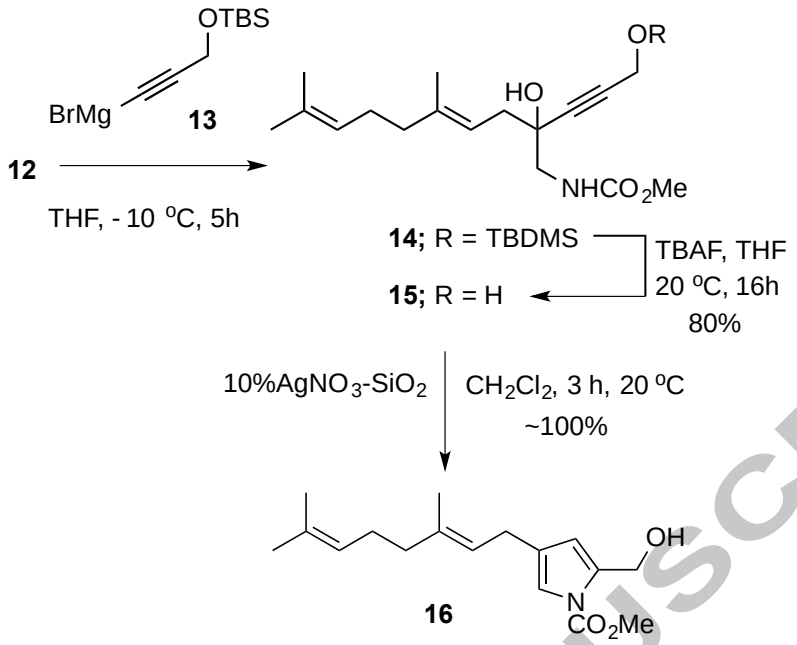
In the event, the first step proceeded smoothly: double deprotonation of the amino-dithiane **9**, crucially in the presence of DMPU,[12] and addition of bromide **5** gave a reproducible 90% yield of the homologous dithiane **11** (Scheme 4). Then the problems began: application of many of the standard dithiane deprotection methods resulted in complete decomposition or generated intractable mixtures. It was only when we realised just how sensitive the desired ketone (**12**) was that we were able to produce it, in essentially quantitative yield, using the established *N*-chlorosuccinimide-silver nitrate method,[13] crucially with a work-up after two minutes at 0 ^{o}C. Remarkably, prolonging the reaction to five minutes resulted in essentially complete decomposition of the desired product, as did silica gel chromatography, which happily was unnecessary.



Scheme 4. The initial steps.

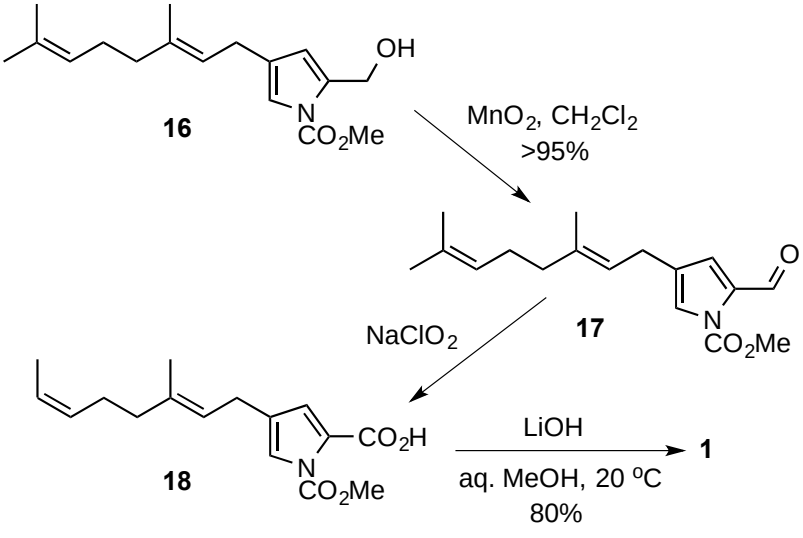
Subsequent nucleophilic addition of *O*-TBS-propargyl alcohol to the ketone **12** gave variable yields of the desired aminoalkyne diol derivative **14**, the best of which was around 85% when using the Grignard species **13** at -10 °C in THF, based on *ca.* 30% recovered ketone **12**, which was separated following rapid silica gel chromatography (Scheme 5). Many alternative metallated alkynes, including lithiated and ceric species, proved less efficient.

We were then horrified to discover that the key aminoalkyne diol **14** was inert to silver nitrate on silica gel (*cf.* Scheme 1). Fortunately, it appeared that this was due to excessive steric crowding, as the corresponding deprotected diol **15** underwent perfectly smooth 5-*endo*-dig cyclisation when exposed to $AgNO_3$-SiO_2 to provide a quantitative yield of the 2-pyrrylmethanol **16** (Scheme 5).[14] However, this did require complete separation from any tetrabutylammonium fluoride and other by-products: it appeared that any residual fluoride had a significant deleterious effect on the subsequent silver-catalysed cyclisation. Due to it also being rather sensitive, there was some loss of the resulting diol **15** during the necessary column chromatographic purification; under optimum conditions (30-100% EtOAc in hexanes), around an 80% yield of very pure material could be recovered.



Scheme 5. Homologation by alkyne addition and the key silver-catalysed step leading to the first pyrrole **16**.

Completion of the synthesis then required oxidation and deprotection. Direct oxidation of the alcohol **16** to the corresponding acid **18** (as its methyl ester) using Corey's MnO_2-NaCN method[15] failed, perhaps because the resulting aldehyde is, in effect, a masked formamide. Happily, a standard two-step combination of MnO_2 and a Lindgren-Pinnick oxidation[16] delivered an excellent overall yield of the 2-pyrrolecarboxylic acid **18**, via the isolated aldehyde **17** (Scheme 6). A final base-induced hydrolysis of the carbamate group then gave Pyrrolostatin **1**, which displayed spectroscopic and analytical data, especially from its ^{13}C spectrum, identical to those recorded previously.[3,10]



Scheme 6. Completion of the synthesis by oxidation.

A new synthesis of Pyrrolostatin **1** has thus been achieved, which delivers the natural product in around 50% overall yield from the known dithiane **9**.

Acknowledgements

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14. *(E)-Methyl 4-(3,7-dimethylocta-2,6-dienyl)-2-(hydroxymethyl)-1H-pyrrole-1-carboxylate* **16**: A solution of (*E*)-methyl 2-hydroxy-2-(3-hydroxyprop-1-ynyl)-5,9-dimethyldeca-4,8-dienylcarbamate **15** (0.12 g, 0.38 mmol) in dry dichloromethane (1 mL) was added to a suspension of 10% silver(I) nitrate on silica gel (0.07 g, 0.04 mmol) in dichloromethane (1 mL), contained in a foil-wrapped flask, and the resulting mixture stirred at ambient temperature for 3 h then filtered through a pad of celite. Evaporation of the filtrate and dichloromethane washings gave *pyrrole* **16** (0.11 g, ~100%) as a pale orange oil, $_{H}$ (400 MHz, $CDCl_3$) 6.95 (1H, s, 5-H), 6.09 (1H, s, 3-H), 5.29 (1H, br. t, *J* = 6.7 Hz, 2'-H), 5.12 (1H, br. t, *J* = 6.8 Hz, 6'-H), 4.64 (2H, s, CH_2OH), 3.97 (3H, s, OMe), 3.70 (1H, br s, OH), 3.10 (2H, d, *J* = 7.2 Hz, 1'-CH_2), 2.16-2.02 (4H, m, 4'- and 5'-CH_2), 1.71 (3H, s, Me), 1.67 (3H, s, Me), 1.63 (3H, s, Me); $_{C}$ (125 MHz, $CDCl_3$) 151.9 (C=O), 136.4 (C), 135.1 (C), 131.5 (C), 126.4 (C), 124.2 (CH), 121.9 (CH), 118.0 (CH), 115.3 (CH), 57.6 (CH_2OH), 54.1 (OMe), 39.6 (1'-CH_2), 26.5 (4' or 5'-CH_2), 25.7 (Me), 25.3 (4'- or 5'-CH_2), 17.7 (Me), 16.0 (Me); $_{max}$/cm^{-1} ($CHCl_3$) 3408, 1733, 1444, 1349, 1280, 1252, 1100; m/z (APCI) 274 (M-H_2O, 100%). Found: M-H_2O, 274.1811. $C_{17}H_{24}NO_2$ requires *M*, 274.1807.

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Graphical Abstract

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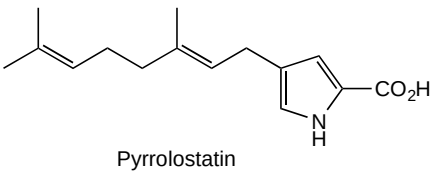

Pyrrolostatin

The major highlights of this total synthesis are:

1. Efficient 2,4-disubstituted pyrrole synthesis by 5-*endo*-dig cyclisation.
2. The approach work to this key precursor is reasonably straightforward.
3. 2,4-Disubstituted pyrroles are quite difficult to obtain regioselectively.
4. The overall yield from an easily-prepared and known precursor is around 50%.