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Total synthesis of kottamide E†
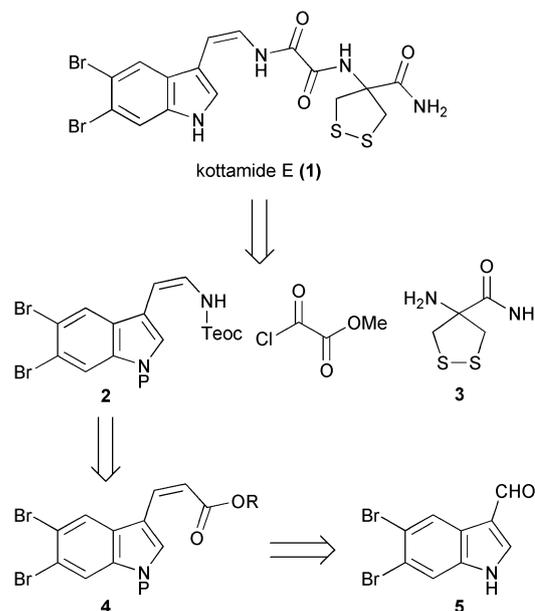
Thomas B. Parsons, Neil Spencer, Chi W. Tsang and Richard S. Grainger*

The first synthesis of kottamide E, a marine natural product containing a 5,6-dibromoindole linked *via* a (*Z*)-enamide to an unusual 1,2-dithiolane-containing amino acid, is reported.

Kottamide E (**1**), isolated as a minor component from the New Zealand ascidian *Pycnoclavella kottae* in 2003 by Appleton and Copp, is the only natural product reported to date containing the unusual 4-amino-1,2-dithiolane-4-carboxylic acid residue.[1] Related mono- and dibrominated *Z*-enamide-containing indole alkaloids, kottamides A–D, isolated from the same source, have been shown to exhibit anti-inflammatory, antitumour and anti-metabolic activities.[2] Given the paucity of the natural product and absence of biological data, we have investigated a total synthesis of kottamide E, which we report herein.

Retrosynthetically we envisaged that union of a protected (*Z*)-enamide **2** with an appropriate oxalic acid derivative and the amide **3** offered a viable approach to kottamide A (Scheme 1). The synthetically challenging, thermodynamically less stable (*Z*)-enamide **2** was planned to arise from reaction of a vinyl isocyanate with 2-trimethylsilylethanol, the isocyanate in turn produced from Curtius rearrangement of an acyl azide derived from α,β-unsaturated ester **4**. We were particularly attracted to this general approach[3,4] to stereodefined enamides given its successful utilization in complex natural product synthesis,[5,6] including indolic enamides.[7] The (*Z*)-double bond geometry within **4** would be set through an appropriate Horner–Wadsworth–Emmons reaction of 5,6-dibromoindole **5**, which we have previously shown can be readily accessed in 3 steps from commercially available methyl indole-3-carboxylate *via* regioselective dibromination.[8–10]

Although the Ando-modified Horner–Wadsworth–Emmons reaction[11] of **5** proceeded with no selectivity, protection of the indole nitrogen gave rise to good to excellent levels of

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. E-mail: r.s.grainger@bham.ac.uk; Fax: +44 (0)121 4144403; Tel: +44 (0)121 4144465

Scheme 1 Retrosynthetic analysis of kottamide E.

stereocontrol in favour of the expected (*Z*)-isomer **7**, which could be readily separated from the corresponding (*E*)-isomer by column chromatography. Attempted ester hydrolysis of **7a–c** was complicated by the faster removal of the indole protecting group and loss of integrity of the alkene double bond geometry. For example, in the case of the Boc-protected indole **7a**, sodium hydroxide caused complete removal of the Boc group after 16 hours at room temperature, with no ester hydrolysis and a small amount of alkene isomerisation. Upon warming to 65 °C saponification was complete within 3 hours but the (*Z*)-alkene was completely converted to its (*E*)-isomer. Similarly the Teoc group of **7b** and the tosyl group of **7c** were removed within 30 and 5 minutes respectively at 0 °C. However, the SEM-protected indole **7d** could be progressed *via* the carboxylic acid to the acyl azide **8** with complete retention of double bond geometry.

Heating **8** in the presence of 2-(trimethylsilyl)ethanol gave the unstable Teoc-protected enecarbamate **9**. This was found to

decompose rapidly, even when stored in the freezer under an atmosphere of argon. *N*-Acylation of **9** *via* deprotonation with NaHMDS and quenching with methyl chlorooxoacetate gave methyl oxoacetate **10**, which was not amenable to purification. Instead, treatment of the crude reaction mixture with TBAF afforded **11** in acceptable yield. Unfortunately the acylation step proved somewhat capricious and was not amenable to scale-up, which required recourse to multiple smaller scale reactions. The combined crude reaction mixtures were subjected to Teoc deprotection to afford **11**, which is stable for several weeks at low temperature. Saponification of **11** gave acid **12** in quantitative yield.

The instability of **10** is consistent with the observations of Kitahara on Teoc-protected enamines appended to indoles, where *N*-acylated products could not be purified until the Teoc-group had been removed.[7] We observed that **10** was highly sensitive to base and that acylation was somewhat reversible: if crude **10** was treated with triethylamine it rapidly reverted to Teoc-protected enamide **9**. It is thought that this is the reason for the modest yield of the acylation-deprotection sequence: the basic nature of TBAF can cause competitive deacylation of intermediate **10** to return **9**.‡

The novel amide **3** was prepared as its hydrochloride salt in 3 steps from the known[12] protected amino acid **13** in 88% overall yield (Scheme 2). Coupling of **13** with carboxylic acid **3** proceeded smoothly using HBTU in DMF at 50 °C over 3 days to afford SEM-protected kottamide E **14** in 66% yield. Unfortunately, clean removal of the SEM group proved to be highly problematic. A wide variety of methods were tested without success.[13] In each case reaction progress was followed by tlc, mass spectrometry and HPLC but we were unable to find conditions to deprotect kottamide E without concomitant fragmentation of the target. In most cases HPLC analysis of the reaction mixture indicated the presence of numerous by-products; mass spectrometric analysis suggested that various mono- and dibrominated fragmentation products were being formed, but sufficient material could not be isolated to confirm the identity of any such by-products.§

Given the difficulties encountered in removing the SEM protecting group from **14** to unveil kottamide E, an alternative approach was devised whereby the potentially sensitive natural product would be accessed directly upon formation of the amide bond. Considering the previously observed labile nature of the tosyl protecting group in **7c** under saponification conditions, this new approach sought to exploit the expected removal of this group alongside methyl ester hydrolysis in the penultimate step (Scheme 3).

Towards this goal, tosyl-protected indole-3-carbaldehyde **6c** underwent Ando-modified Horner–Wadsworth–Emmons reaction[11] to afford (*Z*)-*tert*-butyl ester **17** as the major product, along with the separable (*E*)-isomer (Scheme 3). Hydrolysis of the ester under acidic conditions followed by reaction with DPPA gave acyl azide **18** as a 3.2 : 1 mixture of double bond isomers. Curtius rearrangement and trapping gave protected enamine **19** which was subjected to acylation and immediate deprotection to afford enamide **20**. At this point the unwanted (*E*)-isomer could be removed by flash column chromatography. As expected, removal of the tosyl protecting group and concomitant
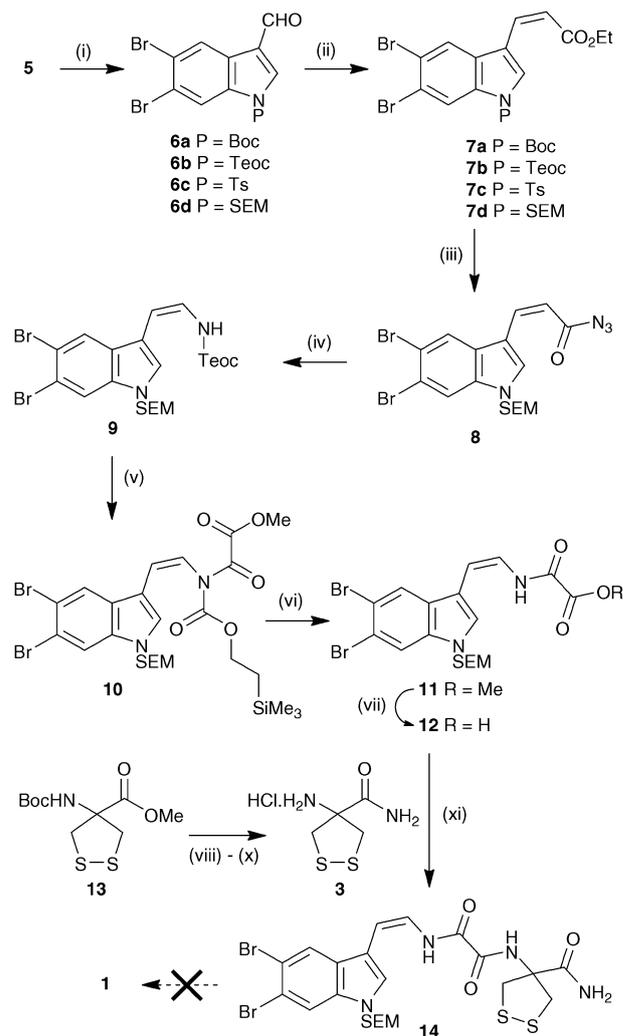
Scheme 2 Synthesis of SEM-protected kottamide E. *Reagents and conditions*: (i) for **6a**: NaH, di-*tert*-butyl dicarbonate, THF, 95%; for **6b**: NaH, 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate, THF, 95%; for **6c**: NaH, TsCl, THF, 81%; for **6d**: NaH, SEMCl, THF, 95%; (ii) EtO₂CCH₂P(O)(OPh)₂, NaH, THF, −40 °C. For **7a**: 81% + 13% (*E*)-isomer; for **7b**: 81% + 13% (*E*)-isomer; for **7c**: 80%; for **7d**: 68% + 31% (*E*)-isomer **15**; (iii) aq. NaOH, MeOH, THF, 65 °C then NaH, DPPA, THF, 91%; (iv) TMSCH₂CH₂OH, toluene, reflux, 77%; (v) NaHMDS, MeO₂CC(O)Cl, THF, 0 °C; (vi) TBAF, THF, 0 °C, 66% over 2 steps; (vii) aq. NaOH, MeOH, THF, 100%; (viii) aq. NaOH, THF, MeOH, 99%; (ix) *i*-BuOC(O)Cl, Et₃N, THF, 0 °C then NH₃, MeOH, −20 °C, 89%; (x) SOCl₂, MeOH, 50 °C, 100%; (xi) HBTU, DMF, Et₃N, 50 °C, 66%.

saponification of the ester moiety of **20** gave carboxylic acid **21**. This was subjected to the previously optimised conditions for amide bond formation with amine **3**. Purification of the reaction mixture required semi-preparative and analytical HPLC to give kottamide E in modest yield and in approximately 85% purity, whose spectroscopic data were in agreement with those reported by Appleton and Cobb.[1,14]

In conclusion, the first total synthesis of kottamide E has been achieved in 8 steps starting from the known dibromoindole **5**, itself prepared in three steps from commercially available methyl indole-3-carboxylate. The successful approach necessitated a change in protecting group strategy, but still suffered from a modest-yielding final step and recourse to purification by HPLC. This, along with the lack of tolerance towards a wide
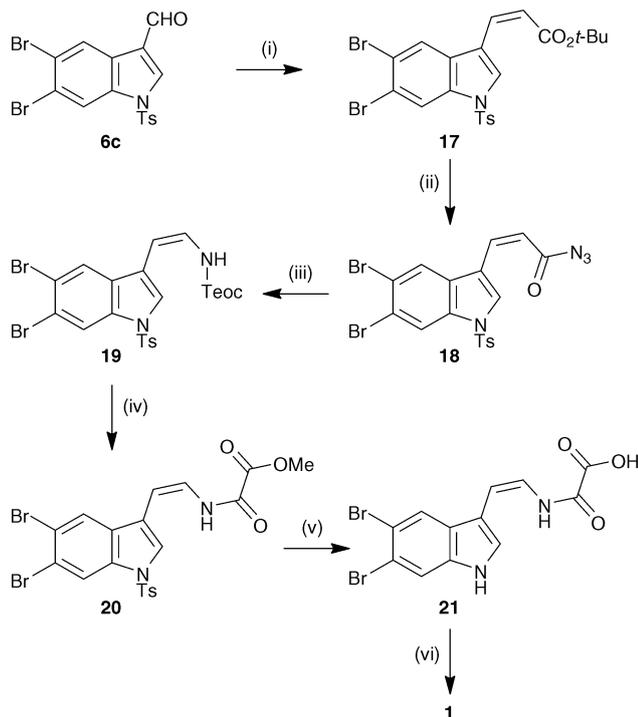
Scheme 3 Total synthesis of kottamide E. *Reagents and conditions*: (i) *t*-BuO₂-CCH₂P(O)(OPh)₂, NaH, THF, −78 °C, 78% + 5% (*E*)-isomer; (ii) TFA, CH₂Cl₂ then NaH, DPPA, THF; (iii) TMSCH₂CH₂OH, toluene, reflux; (iv) NaHMDS, MeO₂CC(O)Cl, THF then TBAF, THF, 32% over 5 steps; (v) aq. NaOH, MeOH, THF, 97%; (vi) **3**·HCl, HBTU, DMF, Et₃N, 38%.

range of SEM deprotection conditions, suggests an inherent sensitivity of the natural product that means the choice of final steps in future syntheses of kottamide E should be of particular concern.

Notes and references

‡ In order to gain further insight into the stability issues, the minor (*E*)-enoate **15** from the Ando-modified Horner–Wadsworth–Emmons

reaction was subjected to the same reaction sequence to give (*E*)-enamide **16** (see ESI† for details). Notably the acylation and Teoc-deprotection steps proceeded smoothly and could be conducted on larger scale than in the (*Z*)-series with no decrease in reaction yield. Presumably this is a reflection of the substantially lower steric crowding around the enamide in the (*E*)-series compared to the (*Z*)-series, where, particularly in the case of **10**, a planar, conjugated arrangement is difficult to achieve. Similarly, reaction of (*Z*)-enamide **9** with TBAF was significantly faster than the corresponding (*E*)-isomer (1 hour at room temperature *vs.* ca. 50% consumption after 2 days), indicating orders of magnitude difference in reactivity between the two double bond isomers.
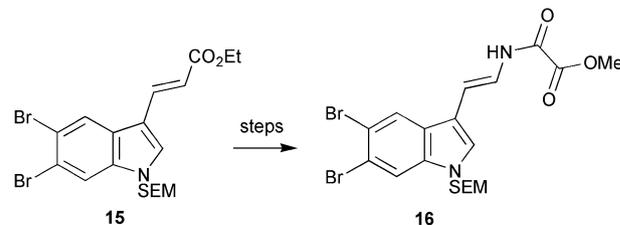
§ The (*E*)-enamide **16** was also progressed to the same stage but the SEM group again could not be cleanly removed to afford the (*E*)-isomer of kottamide E. See ESI† for details.

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13 See ESI† for a complete list of conditions with references.
14 We have been unable to identify the impurities present in the aliphatic region of the NMR spectra of synthetic **1**.