Convergent syntheses of the pyrrolic marine natural products lamellarin-O, lamellarin-Q, lukianol-A and some more highly oxygenated congeners

Martin G. Banwell,*[a] Bernard L. Flynn,[a] Ernest Hamel[b] and David C. R. Hockless[a]

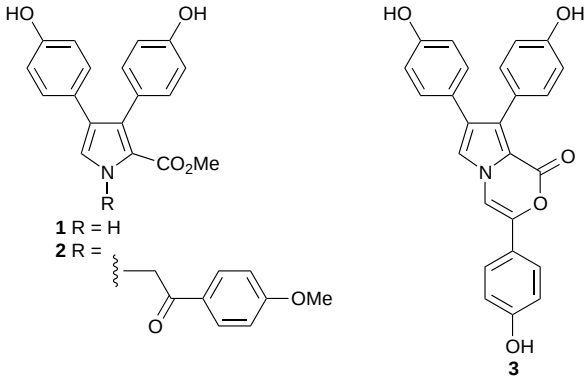
[a] *Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia*

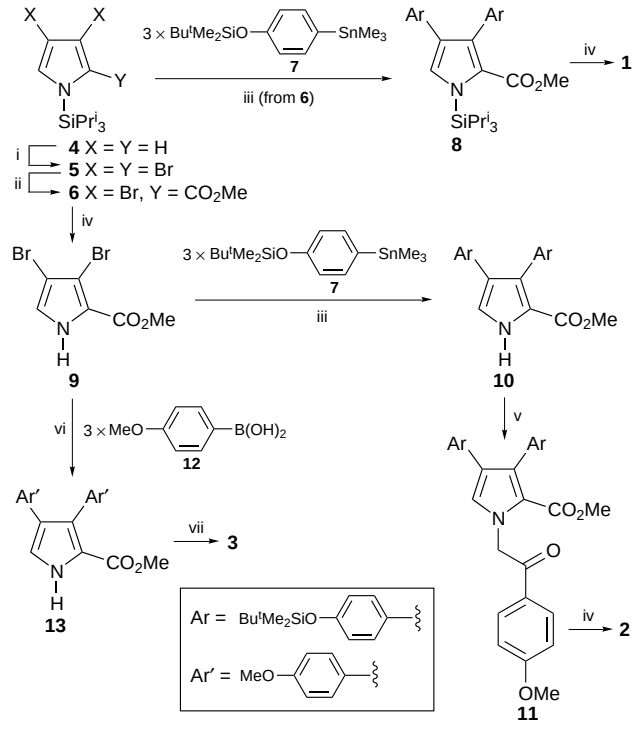
[b] *Laboratory of Molecular Pharmacology, DBS, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA*

The marine alkaloids lamellarin-Q 1, lamellarin-O 2 and lukianol-A 3 as well as their more highly oxygenated congeners 22 and 23 are synthesised using Stille, Suzuki or Negishi cross-coupling reactions as the key step.

Lamellarins A–R,[1–5] lukianols A–B,[6] storniamides A–D,[7] polycitrins A–B[8] and polycitone A[8] are marine natural products that possess a 3,4-diarylated pyrrole 2-carboxylic acid ester or amide moiety as the common structural subunit. These materials have been isolated from widely varying locations and organisms (molluscs, tunicates, sponges) and a number have been shown to possess interesting biological properties. For example, lukianol-A exhibits some activity against a cell line derived from human epidermaoid carcinoma[6] while the penta-*O*-methyl derivative of polycitone A was found to inhibit the growth of SV 40 transformed fibroblast cells at concentrations of 10 μg ml^{-1}.[8] Our own interest in such alkaloids stems from the notion that they are configurationally stable structural hybrids of the powerful anti-mitotic agents combretastatin A-4[9] and colchicine[10] and, as such, may represent new classes of compounds that are capable of inhibiting cell division.[11] Despite the foregoing, remarkably little attention has been given to the total synthesis of any of the above-mentioned marine natural products.[12] Consequently, we now report convergent syntheses of the title compounds **1**–**3** as well as two more highly oxygenated and differentially di-arylated congeners. In each case, the key synthetic step involves Stille[13] or Suzuki[14] or Negishi[15] cross-coupling of readily available pyrrole 2-carboxylic acid derivatives with the appropriate aryl stannane, boronic acid or iodide. These steps represent rare examples of the use of palladium-catalysed cross-coupling chemistry for the introduction of carbon-based substituents onto the pyrrole nucleus.[16]

The pivotal dibromopyrrole **6** (Scheme 1) required for all the syntheses was readily prepared from pyrrole itself using procedures developed by Muchowski and co-workers.[17] Thus, the triisopropylsilyl derivative, **4**,[17] of pyrrole was subjected to reaction with 3 molar equiv. of *N*-bromosuccinimide (NBS) in THF at −78 °C. In this manner the tribromo-derivative, **5** (91%, mp 44–46 °C; lit.,[17] mp 46 °C) was obtained. Subjection of this latter compound to reaction with PhLi followed by $ClCO_2Me$ afforded the previously unreported compound **6** (99%). Stille cross-coupling of pyrrole **6** with 2 equiv. of the Bu^tMe_2Si protected stannane **7** using $Pd(PPh_3)_2Cl_2$ as catalyst gave the expected product **8** (66%). Three-fold deprotection of the tris-*O*-silylether **8** using Bu_4NF then afforded lamellarin-Q **1** (98%, mp 227–228 °C) which was spectroscopically identical with the natural product. The synthesis of lamellarin-O followed very similar lines. Thus, compound **6** was desilylated and the resulting pyrrole **9** (99% mp 147–148 °C) coupled with arylstannane **7**. In this manner the two-fold coupling product **10** (66%) was obtained. Reaction of this latter compound with commercially available 2-bromo-4′-methoxyacetophenone in the presence of base then gave the *N*-substituted pyrrole **11** (84%) which was deprotected with Bu_4NF to provide the natural



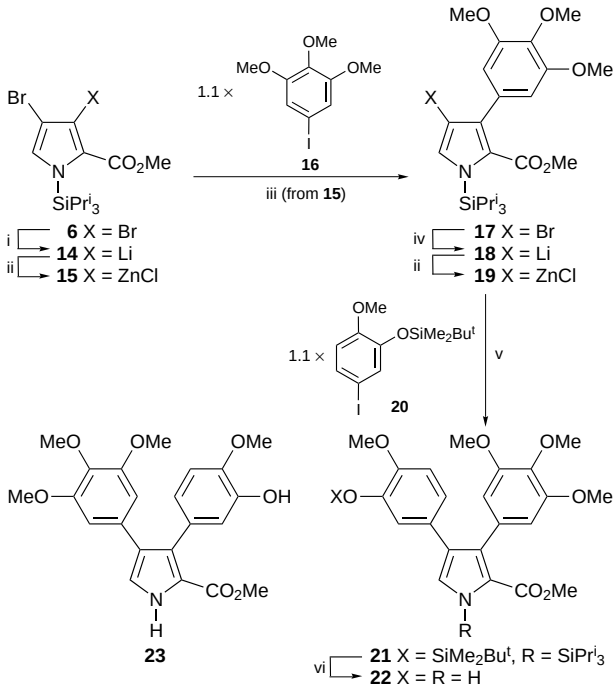


Scheme 1 *Reagents and conditions*: i, NBS (3 equiv.), THF, −78 °C, 1 h then 20 °C for 4 h; ii, PhLi (1 equiv.), −78 °C, 0.16 h then $ClCO_2Me$ (1.05 equiv.), −78 to 20 °C, 1 h; iii, $Pd(PPh_3)_2Cl_2$ (10 mol%), 1,4-dioxane, 101 °C, 14 h; iv, Bu_4NF (10 mol% excess), THF, 20 °C, 1 h then 0.5 M aq. HCl; v, *p*-$MeOC_6H_4COCH_2Br$ (3 equiv.), K_2CO_3 (5 equiv.), Bu_4NCl (20 mol%), THF, 66 °C, 8 h; vi, $Pd(PPh_3)_4$ (5 mol%), sat. aq. Na_2CO_3 (6 equiv.), DMF, 153 °C, 23 h; vii, see ref. 12

product **2** (99%, mp 259–260 °C), the structure of which was confirmed by single-crystal X-ray analysis.†

Two-fold cross-coupling of pyrrole **9** with *p*-$MeOC_6H_4$-$B(OH)_2$ **12**[18] under standard Suzuki conditions afforded compound **13** (78% mp 170–171 °C; lit.,[12] mp 169–171 °C) which has previously been converted, over three steps and in 53% yield, into lukianol A **3** by Fürstner and co-workers.[12] The present work represents a superior synthesis of this natural product since the pivotal intermediate **13** is available in five steps and 69% overall yield from pyrrole by the methods just described while Fürstner's route provides the same material in six steps and *ca*. 15% overall yield.

In carrying out the Stille and Suzuki cross-coupling reactions described above we failed to observe any significant quantities of mono-arylated pyrroles even when shorter reaction times and 1 : 1 stoichiometries were employed. As a consequence, these types of coupling reactions would not seem useful in providing access to differentially di-arylated pyrroles–systems that would be required for the synthesis of the more complex lamellarins and in the preparation of various combretastatin A-4/colchicine hybrids. Such limitations were overcome by regioselective lithiation of compound **6** followed by transmetallation and Negishi cross-coupling reactions as outlined in Scheme 2 for the preparation of differentially diarylated and highly oxygenated pyrroles **22** and **23** (these compounds were chosen as targets because of their structural resemblance to combretastatin A-4). Thus, reaction of compound **6** at −78 °C with PhLi afforded the mono-lithio-derivative **14** which was transmetallated with $ZnCl_2$ to give the organozinc **15**. This last species was, in turn, cross-coupled with the aryl iodide **16**[19] to give the mono-arylated pyrrole **17** (69% from **6**, mp 154–155 °C). Compound **17** was subjected to a further lithiation–transmetallation sequence and intermediate **19** then cross-coupled with aryl iodide **20** (mp 36–38 °C) to give compound **21** (75%, mp 154–156 °C). This latter material was desilylated using Bu_4NF thereby affording the target pyrrole **22** (91%, mp 158–159 °C).



Scheme 2 *Reagents and conditions*: i, PhLi (1.0 equiv.), THF, −78 °C, 0.25 h; ii, $ZnCl_2$ (1.1 equiv.), THF, −78 to *ca*. 20 °C, 0.25 h; iii, Compound **16** (1.1 equiv.), $Pd(PPh_3)_4$ (5 mol%), THF, 20 °C, 8 h; iv, BuLi (equiv.), THF, −78 °C, 0.02 h; v, Compound **20** (1.1 equiv.), $Pd(PPh_3)_4$ (5 mol%), THF, 20 °C, 8 h; vi, Bu_4NF (2.2 equiv.), THF, 20 °C, 1 h then 0.5 m aq. HCl

An exactly analogous reaction sequence where compound **15** was coupled with aryl iodide **20** and the resulting mono-arylated pyrrole (62%) subjected to metallation and coupling with aryl iodide **16** afforded, after deprotection, the isomeric system **23** (42% from **6**, mp 172–173 °C) the structure of which was confirmed by single-crystal X-ray analysis.†

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Footnote

† *Crystal data* for **2**: $C_{30}H_{30}NO_6$, M = 500.57, T = 193(1) K, $P\bar{1}$, a = 10.260(3), b = 11.127(4), c = 12.125(2) Å, α = 108.39, β = 99.97(2), γ = 95.98(2)°, (Z = 2. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallograpic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/295.

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