Synthesis of the pyrrolo[2,3-*c*]carbazole core of the dictyodendrins†‡

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The pyrrolo[2,3-*c*]carbazole 1, the common core of the marine alkaloids known as the dictyodendrins, has been synthesised. The sequence is based on a Suzuki cross-coupling reaction between the pyrrole fragment 2 and the indole fragment 3, followed by tandem photochemical 6π-electrocyclisation/aromatisation.

Dictyodendrins A–E (Fig. 1) are a family of alkaloids isolated from the sponge *Dictyodendrilla verongiformis* that was recently collected off the south Japanese coast.[1] They have a common pyrrolo[2,3-*c*]carbazole core but differ in their respective substituents at the α position of the pyrrole ring and in their oxidation degree. Interestingly, compounds with the same core structure, isolated from a marine sponge of the same genus, have been reported as aldose reductase inhibitors.[2] Dictyodendrins A–E are the first marine natural products with telomerase inhibitory properties, showing 100% inhibition at 50 μg/mL. This enzyme is activated in more than 85% of cancer cells studied to date, but not in normal cells.[3]

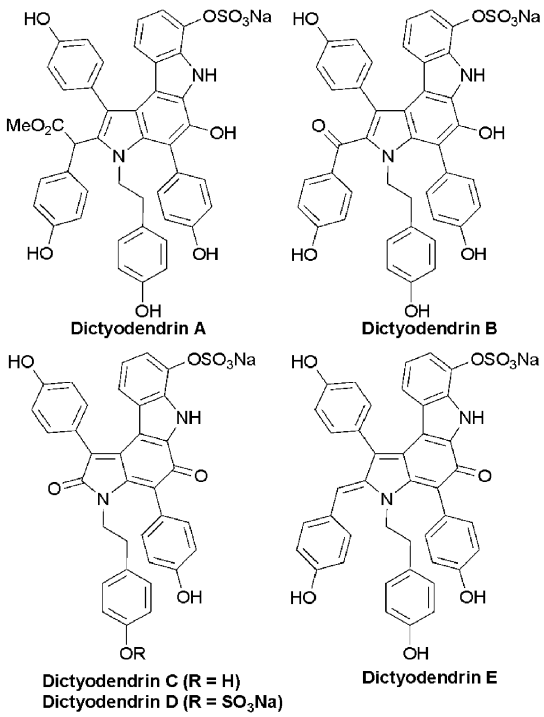
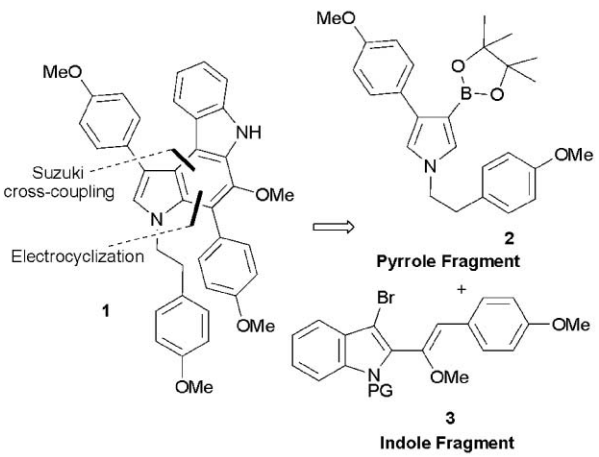


Fig. 1 Structures of dictyodendrins A–E.

Hence, the dictyodendrins are fascinating marine products which could be used as excellent candidates for cancer chemotherapy.

The potent antitumour activity and structural features of dictyodendrins A–E render these marine natural products formidable targets for total syntheses. However, to date, only Fürstner *et al.* have synthesised these compounds.[4] Their strategy consisted of generating the indole nucleus through a titanium-induced reductive ketoamide coupling reaction.[5] This reaction type has already been used by the same group to prepare more complex indole derivatives.[6]

We endeavoured to prepare pyrrolo[2,3-*c*]carbazole **1** as a simplified common core of the dictyodendrins. We envisioned that it would be accessible *via* the bond disconnections shown in Scheme 1. The synthetic strategy employs intermediates **2** and **3** and is based on a Pd(0)-catalysed cross-coupling reaction and a photochemical 6π-electrocyclisation.



Scheme 1 Retrosynthetic analysis of pyrrolo[2,3-*c*]carbazole core **1**.

The synthesis began with construction of the pyrrole fragment **2** from the corresponding halo derivatives **9** and **10**, which were prepared *via* halogenation, deprotection and subsequent alkylation of **6** (Scheme 2). The procedure described below, based on using a boronic ester instead of a boronic acid, provided much higher

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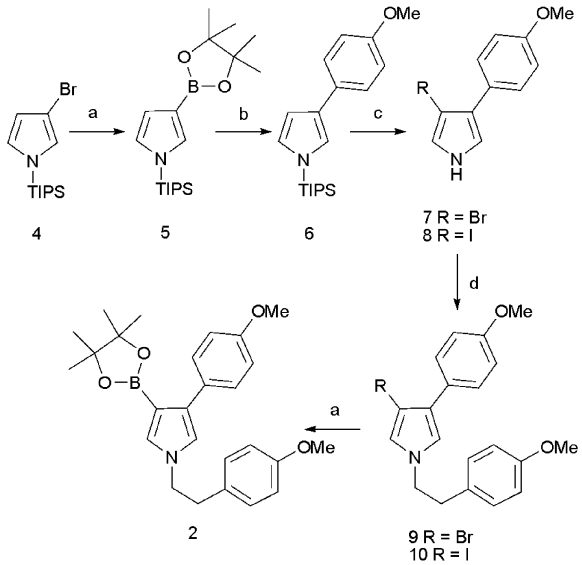
† Dedicated to Professor Josep Font on the occasion of his retirement from the Universitat Autònoma de Barcelona

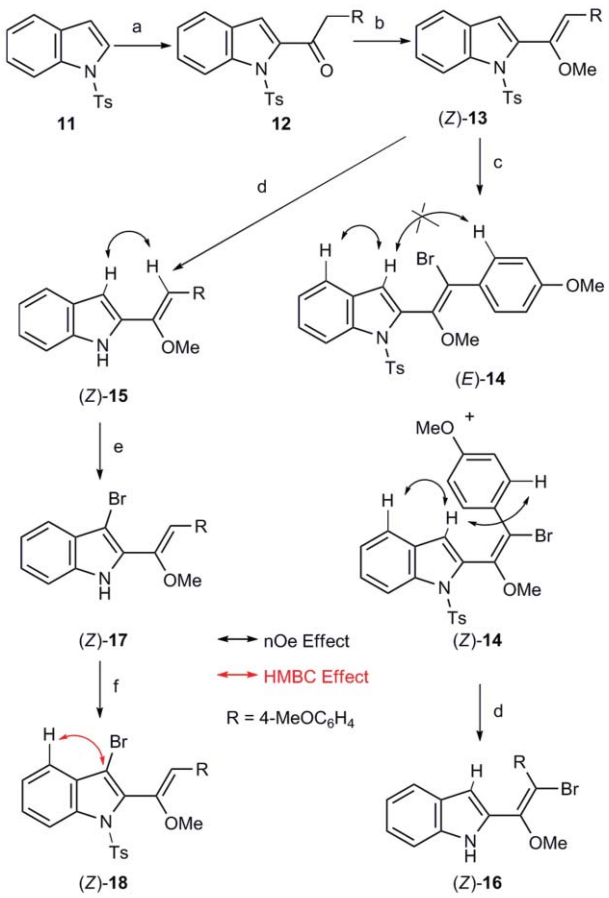
‡ Electronic supplementary information (ESI) available: Full experimental procedures and spectroscopic data for all new compounds. Crystallographic information file (CIF) of (*Z*)-**14**. CCDC reference number 704582. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b822933n



Scheme 2 Synthesis of the pyrrole fragment **2**. *Reagents and conditions:* (a) *n*-BuLi, THF, −78 °C; then 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; (b) *p*-bromoanisole, $Pd(PPh_3)_4$, Na_2CO_3, MeOH/toluene, reflux, 81% (2 steps from **4**); (c) NBS, THF, −78 °C-RT; then TBAF, THF, RT, 13–52% of **7** (2 steps from **6**) or I_2, $Hg(OAc)_2$, CH_2Cl_2, −78 °C; TBAF, THF, RT; (d) 4-methoxyphenethyl bromide, K_2CO_3, DMF, 80 °C, 90% of **9**, 49% of **10** (3 steps from **6**).

yield (81% *vs*. 60%) than that obtained in previous reports[7] of the synthesis of **6**. Pyrrole **6** was prepared by Suzuki cross-coupling between *p*-bromoanisole and pyrrole boronic ester **5**,[8] which had been previously synthesised from **4**[9] by bromine-lithium exchange followed by reaction with commercially available 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.[10] Although *N*-alkylation of **7** with 4-methoxyphenethyl bromide in DMF using K_2CO_3 as a base at 80 °C led to the desired target **9** in good yield (90%),[11] bromination of **6** with 1 equiv. of NBS in THF at −78 °C followed by deprotection with TBAF gave **7** in variable yields,[12] probably due to competitive bromination at the pyrrole 2 position,[13] which afforded the very unstable 2-bromo-3-(4-methoxyphenyl)pyrrole as a minor byproduct. To prevent formation of the said byproduct, we sought an alternative route for the introduction of a bulky halogen. Thus, we studied formation of the iodide derivative **10**. **6** was iodinated with iodine in the presence of mercuric acetate at −78 °C using equimolar quantities of the three reactants. In these conditions, only the 3-iodo compound was isolated. TBAF deprotection, followed by *N*-alkylation, provided **10** in 49% overall yield. Finally, **2** was synthesised from **10** by employing the same conditions used to prepare **5**.

The indole fragment was assembled from ketone **12**, which had been previously obtained by our group (Scheme 3).[14] The enol ether (*Z*)-**13** was obtained in 78% yield by reaction of **12** with NaH and dimethyl sulfate in DMF.[15] We expected that bromination of the enol ether (*Z*)-**13** with NBS in THF at −78 °C and subsequent warming to room temperature would give (*Z*)-**18**, the brominated product at the indole 3 position. However, these conditions led to a stereoisomeric mixture of bromides (*Z*)-**14** and (*E*)-**14** in a 2.6:1 ratio (as determined by peak area [HPLC and ^{1}H-NMR]). Selective crystallisation of this



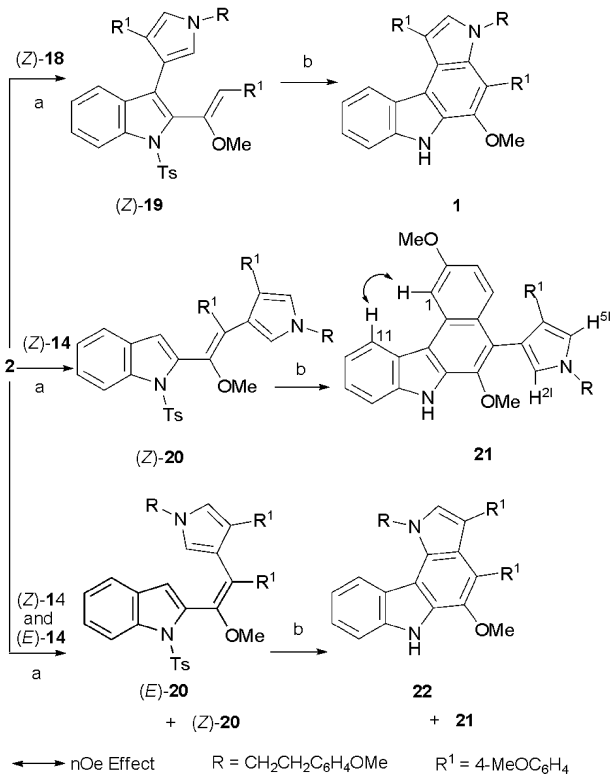
Scheme 3 Synthesis of the indole fragment (*Z*)-**18**, with the nOe and HMBC effects of selected compounds shown. *Reagents and conditions:* (a) *n*-BuLi, THF, −78 °C; then Me_3SnCl, RT; then 4-$MeOC_6H_4CH_2COCl$, $PdCl_2(PPh_3)_2$, CuI, toluene, reflux, 65%; (b) $(MeO)_2SO_2$, NaH, DMF, 78%; (c) NBS, THF, −78 °C–RT; (d) Cs_2CO_3, THF/MeOH, 60 °C, 98% of (*Z*)-**15**, quant. of (*Z*)-**16**; (e) NBS, NaOMe, MeOH, RT; (f) NaH, TsCl, THF, 0 °C–RT, 72% [2 steps from (*Z*)-**15**].

mixture with acetonitrile gave (*Z*)-**14**. The absolute configuration of (*Z*)-**14** was established by NOESY experiments and X-ray analysis.[16] Semipreparative HPLC was used to obtain pure (*E*)-**14**, whose stereochemistry was determined by NMR studies (See ESI‡).[17]

To increase the reactivity of the indole, a deprotection–bromination–protection sequence was planned for the preparation of (*Z*)-**18**. Elimination of the tosyl protecting group of (*Z*)-**13**, using the mild and convenient method described by Bajwa *et al*.,[18] provided (*Z*)-**15** in 98% yield.[19] Subjecting (*Z*)-**14** to similar reaction conditions, (*Z*)-**16** was obtained in quantitative yield.[20] Reaction of (*Z*)-**15** with NBS in the presence of sodium methoxide in methanol,[21] followed by protection with TsCl, afforded the desired brominated product (*Z*)-**18**[22] in 72% overall yield. Furthermore, the regioselectivity of the bromination to obtain (*Z*)-**17** from (*Z*)-**15** was corroborated by ^{1}H/^{1}H COSY experiments.[23]

Once **2** and (*Z*)-**18** were prepared, we began the final stage of the synthesis of the pyrrolo[2,3-*c*]carbazole core: Suzuki cross-coupling reaction of the two fragments followed by

6π-electrocyclisation.[24] Thus, the Pd(0)-catalysed reaction of (*Z*)-**18** with the pyrrole boronic ester **2** afforded (*Z*)-**19** in 59% yield. The final step involved 6π-electrocyclisation of (*Z*)-**19** by irradiation with a medium pressure Hg-lamp (125 W) in acetonitrile. Aromatization by addition of Pd/C and nitrobenzene[25] to the reaction medium afforded the desired pyrrolo[2,3-*c*]carbazole **1** in 25% yield. Similarly, Suzuki reaction between **2** and (*Z*)-**14** led to (*Z*)-**20** in 67% yield, which was then subjected to 6π-electrocyclisation to provide **21** in 17% yield.[26] This reaction sequence was also used with the stereoisomeric mixture of indoles (*Z*)-**14** and (*E*)-**14** to obtain compound **22**, a regioisomer of **1** (Scheme 4). The Pd(0)-catalysed reaction of **2** with the mixture of indoles (*Z*)-**14** and (*E*)-**14**, followed by 6π-electrocyclisation, gave the benzo[*c*]carbazole **21** and the pyrrolo[3,2-*c*]carbazole **22** in 13% and 4% overall yields, respectively.



Scheme 4 Suzuki cross-coupling reactions and 6π-electrocyclisations (with nOe effect shown). *Reagents and conditions:* (a) $Pd(PPh_3)_4$, Na_2CO_3, DMF, reflux; then (*Z*)-**18**, 59% of (*Z*)-**19** or then (*Z*)-**14**, 67% of (*Z*)-**20** or then (*Z*)-**14** and (*E*)-**14**; (b) *hν*, CH_3CN, $C_6H_5NO_2$, Pd/C, 25% of **1**, 17% of **21**, 4% of **22** and 13% of **21** [2 steps from (*Z*)-**14** and (*E*)-**14**].

In summary, we have synthesised the pyrrolo[2,3-*c*]carbazole **1**, a simplified common dictyodendrins core, using a convergent strategy based on a Pd(0) catalysed cross-coupling reaction and a 6π-electrocyclisation. Furthermore, more complex indole structures, such as benzo[*c*]carbazole **21** and pyrrolo[3,2-*c*]carbazole **22**, were also prepared.

Acknowledgements

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