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An Expeditious Synthesis of Structural Analogs of the Marine Cytotoxic Agents Grossularines-1 and -2[1]

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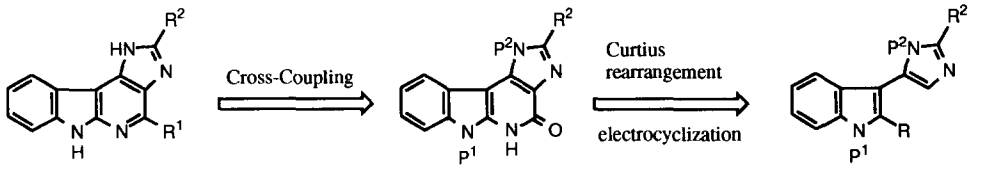
Abstract: A short access to 2-carbethoxy-3-(5-imidazolyl)indoles (**13**, **14**, **16**), featuring Pd-catalyzed cross coupling between 3-iodoindoles (**10–12**) and imidazolostannane (**9**) has been developed. These derivatives when subjected to tandem modified Curtius rearrangement-intramolecular electrocyclization led to the pyridones (**19–23**) which are key intermediates in the synthesis of the analogs (**31**), (**33**) and (**36**) of the naturally occurring cytotoxic α-carbolines grossularines-1 and -2 (**1**,**2**).

Recently, we reported a convergent and general approach to pyrido[2,3-*b*]indoles based on intramolecular cyclization of suitably functionalized anilino-pyridines, the preparation of which involved palladium-mediated aryl-coupling as a key step. This approach has led to the first synthesis of the fused tetracyclic subunit[2] **3**, a common structural feature of the marine cytotoxic agents grossularine-1 **1** and grossularine-2[3] **2** (Scheme 1). In an effort to develop an even shorter and possibly more flexible route to analogs (*i.e.* **4**) of these natural products, we explored an alternative strategy, retrosynthetically depicted in scheme 1, whereby the key fused pyridone **5** would be constructed through Curtius rearrangement of acid **6** and *in situ* intramolecular electrocyclization of the intermediate isocyanate **7**. These pyridones would then be elaborated further into the target compounds **4** through a sequence involving triflate formation and subsequent arylation by way of the Stille[4] or Suzuki[5] cross-coupling methodologies with or without carbon monoxide insertion (Scheme 1).



1 Grossularine-1: R^1 = 3-acylindole, R^2 = NMe_2
2 Grossularine-2: R^1 = p-HOC_6H_4CO, R^2 = NMe_2
3 R^1 = Cl, R^2 = NMe_2
4 R^1 = Ar, ArCO; R^2 = H

5; P^1,P^2 = protecting groups

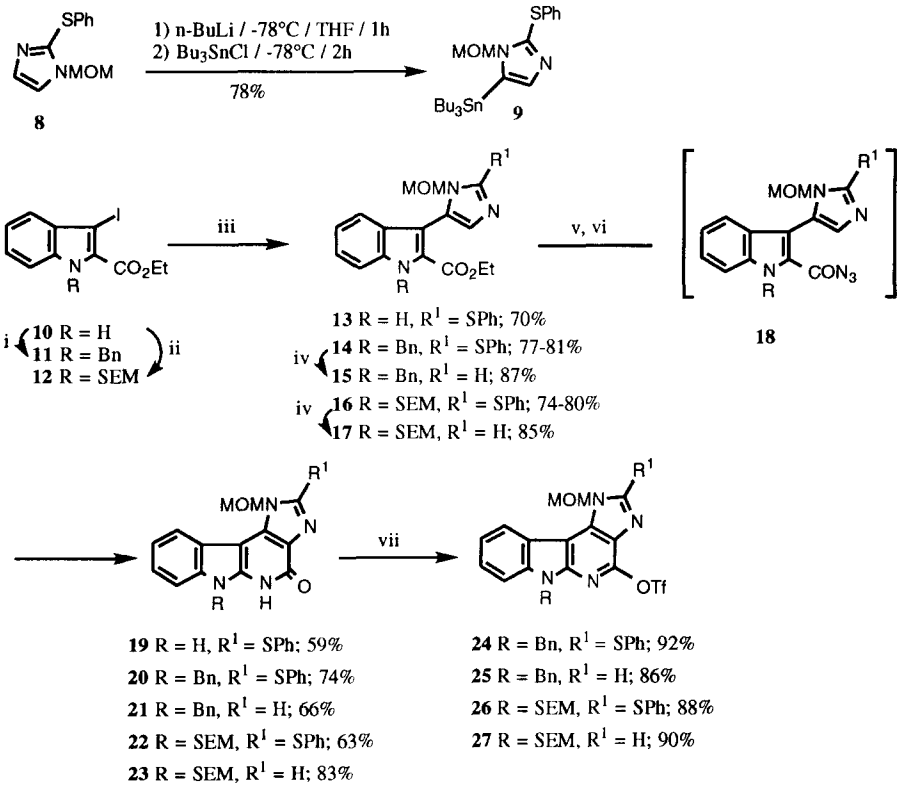
6 R = COOH
7 R = NCO

Scheme 1.

At the time we began this work only two examples of a related approach describing the synthesis of indoloquinolinones via thermal electrocyclization of 3-phenyl-indol-2-ylcarbamates or 3-phenyl-2-carboxazidoindoles were recorded in the literature.[6]

The implementation of this strategy rested upon ready access to 2-carboxyl-3-(5-imidazolyl)indole **6** the synthesis of which was envisaged through Pd-mediated cross-coupling between a 3-haloindole derivative and an imidazolostannane. In recent years, heterocycles introduction at C-3 of indole via transition-metal catalyzed C–C bond formation involving either 3-haloindoles[7] or 3-indolyl-metal[8] has attracted much interest because of its simplicity and directness. It is only very recently, however, that the imidazole nucleus was implicated in such a transformation.[1,9]

Our synthesis started with the preparation of the imidazolostannane **9** which was obtained in a straightforward manner by C-5 metallation of the known imidazole[10] **8** according to Iddon[11] and quenching with n-Bu3SnCl (Scheme 2).

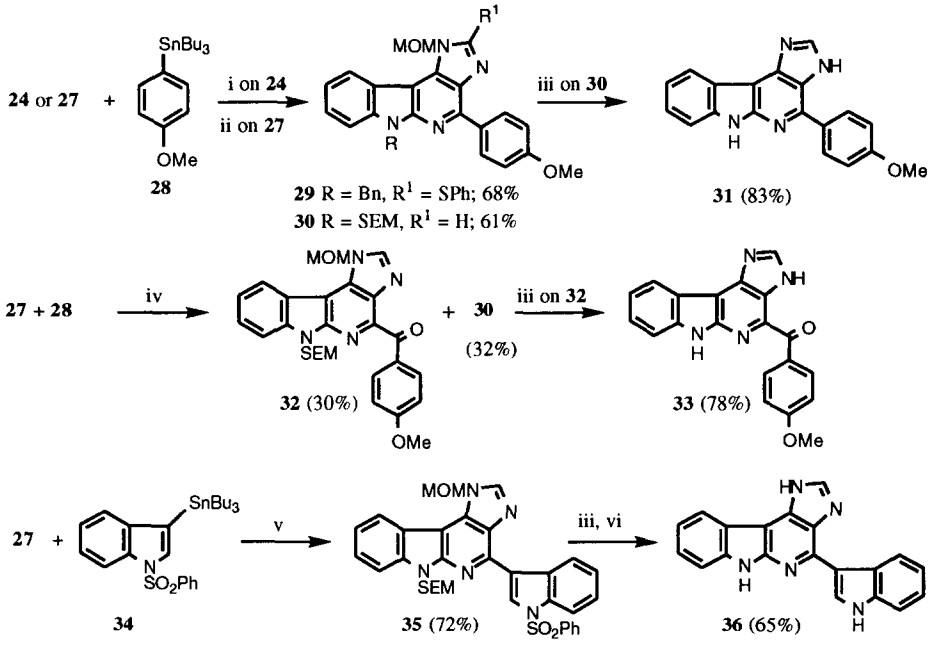


Scheme 2. *Reagents and conditions*: i) BnBr, NaH, DMF, 0°C then rt overnight, 95%; ii) NaH, DMF, SEMCl, 0°C, 3h, 93%; iii) **9**, $Pd(PPh_3)_2Cl_2$ (6mol%), DMF, 120°C, 2h; iv) Rancy-Ni, EtOH, reflux, 5h; v) xsLiOH, THF-H_2O-MeOH, rt, 6h, 85-93%; vi) DPPA, Et_3N, DMF, 0°C then 80°–130°C, 1h; vii) Tf_2O, pyridine, 0°C then rt overnight.

Coupling of stannane **9** with the known[12] 3-iodoindole **10** or its derivatives **11** and **12** in the presence of catalytic Pd(PPh3)2Cl2 in DMF gave the expected 3-imidazoloindoles **13**, **14** and **16** respectively in good yields on a multigram scale. 3-Imidazoloindoles unsubstituted at C-2 have also been obtained in this way.[13] At this stage the thiophenyl group, which served its role of protecting the position 2 of the imidazole nucleus, was removed by Raney nickel reduction to afford compounds **15** and **17** in good yields. Hydrolysis of the ester

function in compounds **13–17** was carried out using LiOH as base giving the corresponding acids in 87–95% yield. These acids were then subjected to the modified Curtius rearrangement procedure of Yamada[14] to provide the corresponding acylazides **18**. Although these somewhat unstable intermediates have on occasions been isolated, the tandem Curtius rearrangement–electrocyclization was more conveniently carried out in a one-pot reaction by heating in DMF. The key pyridones **19–23** were thus obtained in fairly good yields and subsequently transformed into the triflates **24–27** by exposure to triflic anhydride in pyridine (Scheme 2).

Coupling of triflate **24** with stannane **28**[15] using $Pd(PPh_3)_4$ as catalyst and excess LiCl in refluxing toluene furnished compound **29**, whereas coupling of triflate **27** required the use of DMF as solvent and $PdCl_2(PPh_3)_2$ as catalyst to deliver compound **30** which in turn was converted to the α-carboline **31** upon acid treatment. The α-carboline **32** was similarly obtained together with compound **30** when the reaction was conducted in the presence of carbon monoxide. Deprotection of **32** under acidic conditions gave the analog **33** of grossularine-2[16] in good yield. Finally, cross-coupling between triflate **27** and stannane **34**[17] yielded the bis-indole **35**, the deprotection of which led to the analog **36** of grossularine-1 (Scheme 3).



Scheme 3. *Reagents and conditions*: i) $Pd(PPh_3)_4$ (5mol%), LiCl (3eq), PhMe, reflux, 10h; ii) $PdCl_2(PPh_3)_2$ (5mol%), DMF, LiCl (3eq), 100°C, overnight; iii) 3M HCl, EtOH-H_2O, 90°C, 3h; iv) $Pd(PPh_3)_2Cl_2$ (5mol%), CO, LiCl (3eq), DMF, 100°C, 12h; v) $Pd(PPh_3)_4$ (5mol%), LiCl (3eq), DMF, 100°C, 10h; vi) 10% aq.NaOH-EtOH (1:2), reflux,overnight.

In this work we have been able to develop a short and convenient synthesis of 3-imidazoloindole derivatives (*i.e.* **13–17**) whose two-step conversion into the indolopyridones **19–23** provided a concise and potentially versatile access to analogs[18] of the natural antitumor compounds grossularines-1 and -2. Further application of this chemistry to the synthesis of other marine natural products is currently under way, the details of which will be reported in due course.

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References and Notes

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16. While this manuscript was under preparation Professor Hibino kindly informed us that he had recently completed the synthesis of grossularine-2 via a similar approach.
17. This compound was prepared from 1-phenylsulfonyl-3-bromoindole through metal-halogen exchange and quenching with n-Bu_3SnCl see, Hodson, H.F.; Madge, D.J.; Slawin, A.N.Z.; Widdowson, D.A., Williams, D.J. *Tetrahedron* **1994**, *50*, 1899-1906.
18. All compounds gave spectroscopic data in agreement with the assigned structures.

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