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# A short route to functionalized imidazo[4,5-*c*]carbazoles. Synthesis of the first example of the imidazo[4,5-*c*]β-carboline ring system

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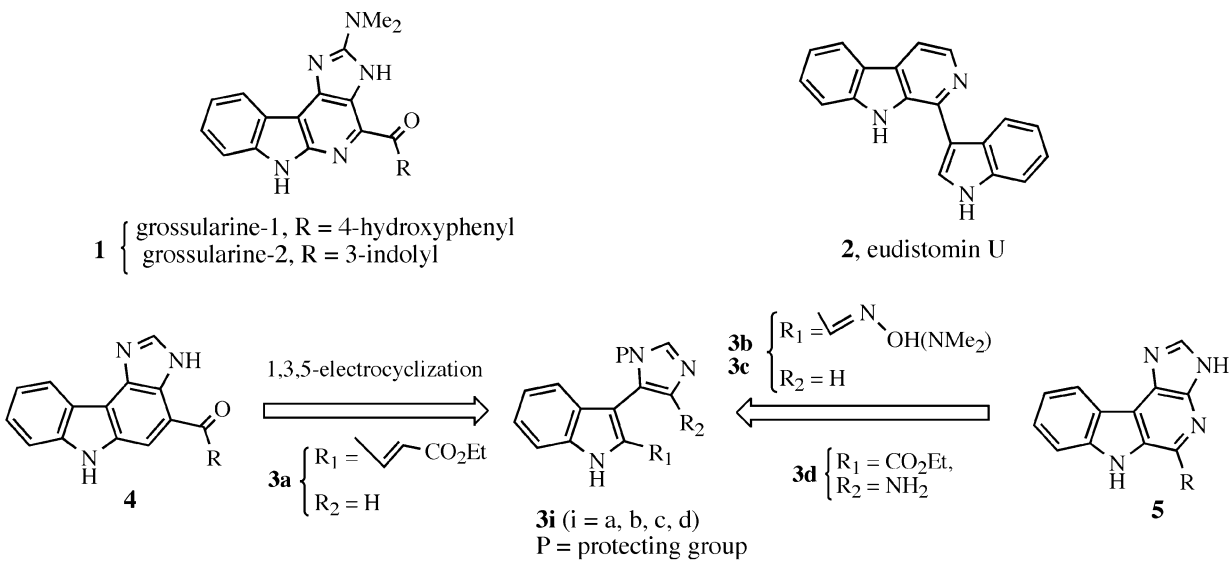
**Abstract**—A new synthetic route to functionalized imidazo[4,5-*c*]carbazoles (**4**) via intramolecular electrocyclization of indolo-1,3,5-hexatriene system (**3a**) is described. Thermally induced ring-closure of 2-ethylcarboxylate-(4-amino-5-imidazolyl)-3-indole (**3d**) led to the previously unknown imidazo[4,5-*c*]β-carboline ring system (**5**). These heterocycles were efficiently converted into analogs of both the marine cytotoxic agents grossularines-1 and -2 (**1**) and the antimicrobial alkaloid eudistomin U (**2**). 

The carbazole and β-carboline moieties are important structural subunits which occur as components of many biologically interesting, natural as well as non-natural, compounds.[1]

As part of an investigation into the synthesis of structurally related derivatives of the marine cytotoxic α-carbolines, grossularines-1 and -2[2] (**1**, Scheme 1), we were interested in developing a ready access to carbazole and β-carboline containing analogs of both these natural products and the antimicrobial alkaloid eudistomin U (**2**).[3]

Previous synthesis of imidazo[4,5-*c*]carbazole[4] has made use of a 3-amino-carbazole derivative as starting material, which was elaborated further into the target




**Scheme 1.**

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heterocycle via regioselective nitration and subsequent imidazole ring construction. In recent years, the thermal- and photo-induced electrocyclizations of 1,3,5- or 1-aza-3,5-hexatrienes have provided an efficient alternative method for accessing the carbazole and β-carboline ring systems,[5] respectively. We report herein the application of such a methodology to the 2-acrylate-3-imidazolylindole derivative **3a** en route to the corresponding imidazolocarbazole **4** (Scheme 1).

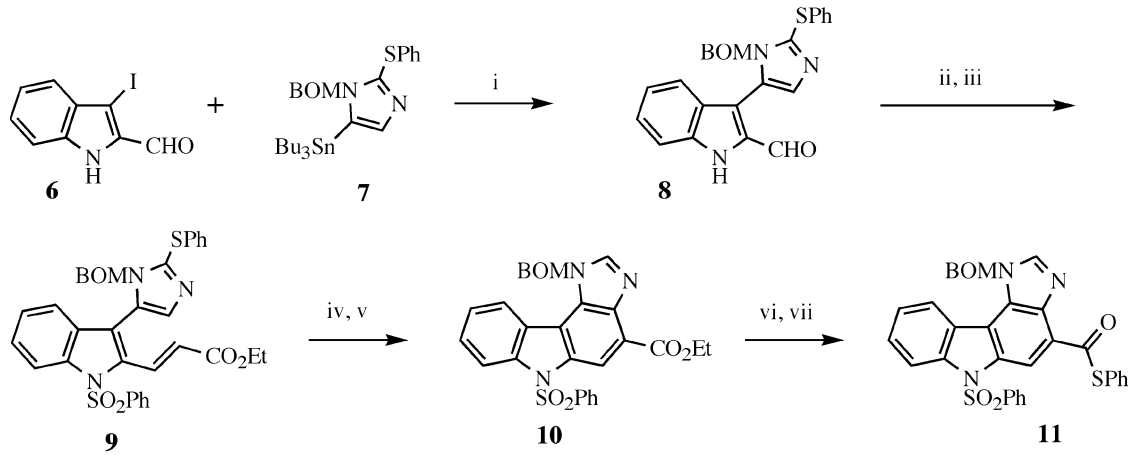
The conversion of 2-vinyl-3-imadazoloindole **9** into carbazole **10** was first attempted. Access to compound **9** involved Stille cross-coupling of 2-formyl-3-iodoindole[6] **6** with imidazolostannane **7** by a route similar to that we reported previously[7] to furnish the expected imidazoloindole **8** in good yield.

Wittig reaction of aldehyde **8** gave the 2-vinyl compound **9** which in turn was transformed, in good yield, into the corresponding carbazole **10** through a one-pot two-step process involving electrocyclization followed by in situ aromatization with $MnO_2$ and Raney-nickel desulfurization (Scheme 2).

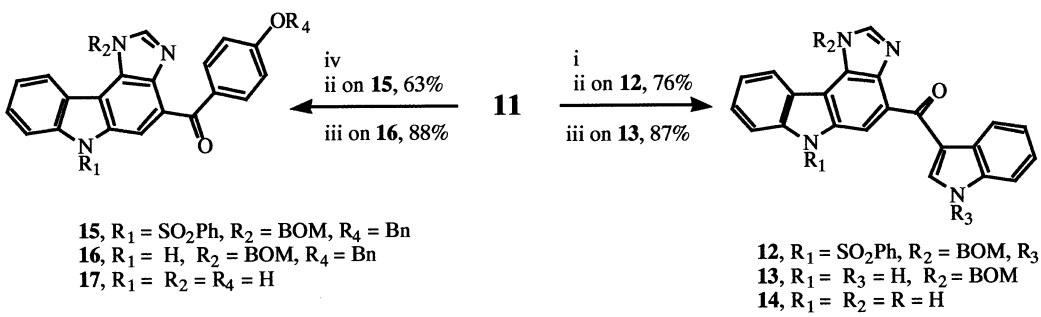
Finally, conversion of ester **10** into the requisite ketones **14** and **17** was carried out by using the thiolester–boronic acid cross-coupling approach[8] recently reported by Liebeskind and Srogl.

To this end, thiol ester **11** was obtained in a straightforward manner by saponification of **10** and treatment of the resulting acid with carbonyl-diimidazole and thiophenol.[9] The thiol ester **11** was then subjected to palladium-catalyzed cross-coupling with the known 1-tosyl-3-indoleboronic acid[10] **31** (Scheme 4) to provide ketone **12** in a modest 55% yield. Deprotection of **12** under standard conditions furnished the analog **14** of grossularine-2 (**1**) in good yield. The analog **17** of grossularine-1 (**1**) was similarly obtained through cross-coupling with 4-benzyloxyphenylboronic acid[11] **28** and subsequent deprotection of ketone **15** (Scheme 3).

With carbazoles **14** and **17** in hand, we then turned our attention to the synthesis of their β-carbolines counterparts. Our synthetic efforts toward this end focused initially on the transformation of oxime **3b** ($R_1$ = CHNOH, $R_2$ = H) and hydrazone **3c** ($R_1$ = $HCNNMe_2$, $R_2$ = H), respectively, into the β-carboline ring-system through thermal electrocyclization.[12,13] Compounds **3b** and **3c** failed, however, to undergo thermal electrocyclization, suffering instead extensive decomposition.



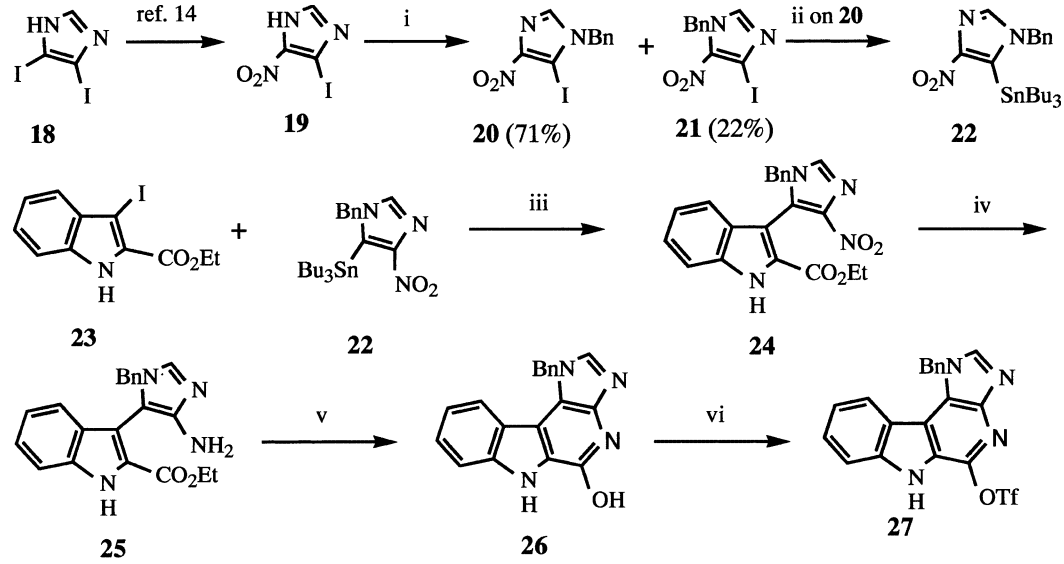

**Scheme 2.** *Reagents and conditions*: (i) **7** (1.5 equiv.), $PdCl_2(PPh_3)_2$ (6 mol%), DMF, 120°C, 2.5 h, 75–80%; (ii) NaH (1.3 equiv.), THF, $(EtO)_2P(O)CH_2CO_2Et$, 0°C, 15 min, add **8** (0.55 equiv.), 0°C then rt, 2 h, 93%; (iii) NaH (1.1 equiv.), DMF, 0°C, 30 min, $PhSO_2Cl$ (1.2 equiv.), 0°C then rt, 2 h, 71%; (iv) *o*-$Cl_2Ph$, reflux, 1 h, then add $MnO_2$ (8 equiv.), reflux, 1 h, 72%; (v) Raney-Ni (xs), EtOH–THF (2:1), reflux, 2 h, 84%; (vi) LiOH (7 equiv.), THF:$H_2O$:MeOH (5:2:1), rt, 5 h, 91%; (vii) CDI (1.9 equiv.), DMF, −10°C, 2 h, then PhSH (xs), −10°C, 2 h, 58%.




**15**, $R_1$ = $SO_2Ph$, $R_2$ = BOM, $R_4$ = Bn
**16**, $R_1$ = H, $R_2$ = BOM, $R_4$ = Bn
**17**, $R_1$ = $R_2$ = $R_4$ = H

**12**, $R_1$ = $SO_2Ph$, $R_2$ = BOM, $R_3$ = Ts
**13**, $R_1$ = $R_3$ = H, $R_2$ = BOM
**14**, $R_1$ = $R_2$ = R = H

**Scheme 3.** *Reagents and conditions*: (i) **31** (1.1 equiv.) CuTc (1.5 equiv.), $Pd_2dba_3{\cdot}CHCl_3$ (1.2 mol%), trifurylphosphine (10 mol%), THF, 50°C, 18 h, 55%; (ii) 10% aq. KOH, THF:EtOH (2:1), reflux, 4 h; (iii) Pd/C (10%), $HCO_2^-NH_4^+$, EtOH, reflux, 3 h; (iv) **28** (2 equiv.), CuTc (3 equiv.), $Pd_2dba_3{\cdot}CHCl_3$ (3 mol%), trifurylphosphine (26 mol%), THF, 50°C, 18 h, 60%.



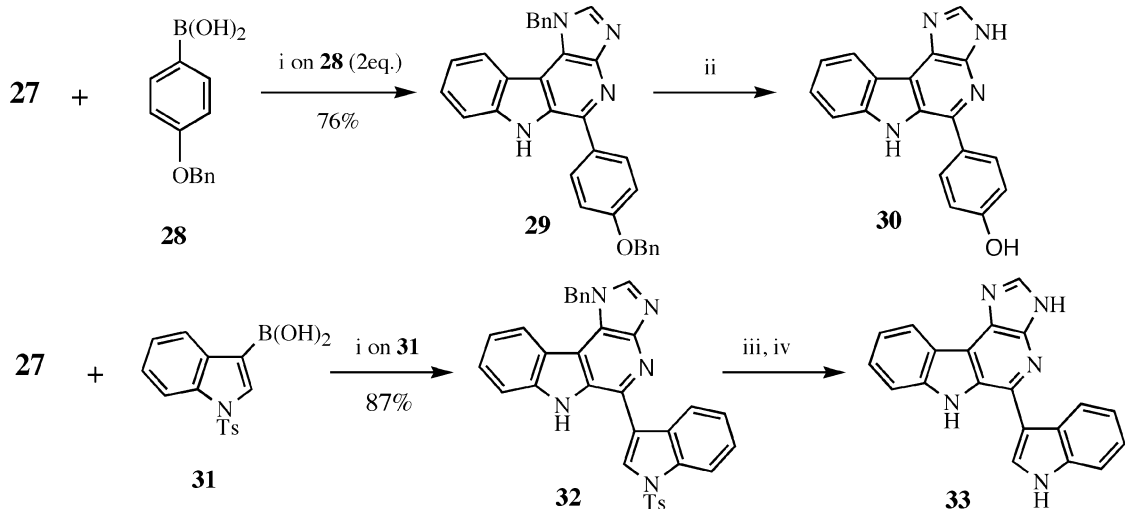

**Scheme 4.** *Reagents and conditions*: (i) $K_2CO_3$, MeCN, BnBr, reflux, 3 h; (ii) $(n\text{-}Bu_3Sn)_2$, $PdCl_2(PPh_3)_2$, DMF, 120°C, 2 h, 57%; (iii) **23** (1.2 equiv.), $Pd(PPh_3)_4$ (4 mol%), CuI (8 mol%), DMF, 80%, 2.5 h, 62%; (iv) Raney-Ni, $H_2$, MeOH, rt, 2.5 h, 64%; (v) $o\text{-}Cl_2C_6H_4$, reflux, 48 h, 79%; (vi) $Tf_2O$, pyridine, 0°C, 30 min, rt, overnight, 87%.

Accordingly, an alternative access to the imidazolo-β-carboline ring system was sought, based on thermally-induced ring closure of 2-ethylcarboxylate-3-(4-amino-5-imidazolyl)-indole **25** (Scheme 4). Synthesis of **24**, the precursor of **25**, was envisaged through coupling of imidazolostannane **22** with 3-iodoindole[6] **23** (Scheme 4).

Protection of the known (4,5)-iodonitroimidazole[14] **19** by way of *N*-benzyl derivatives formation[15] led to a mixture of compounds **20** and **21**, the purification of which allowed efficient recovery of isomer **20** subsequently transformed into stannane **22**.

Cross-coupling of stannane **22** with iodoindole **23** furnished the expected 2-ethylcarboxylate-3-(4-nitro-5-imidazolyl)indole **24**, the subsequent reduction of which gave 4-amino derivative **25**. Intramolecular ring-closure of **25** required prolonged heating in refluxing *o*-dichlorobenzene to provide pyridone **26**, which was then transformed into triflate **27** upon exposure to triflic anhydride in pyridine. Coupling of triflate **27** with boronic acids **28** and **31** provided the analogs **29** and **32**, which upon routine deprotection furnished the analogs **30** and **33** of eudistomin U (**2**) (Scheme 5).[16]

In the course of this work we have been able to develop a new short approach toward the functionalized imidazo[4,5-*c*]carbazoles **10** and have, as well, achieved the first synthesis of the previously unknown imidazolo-β-carboline ring system **26**. In addition, these heterocycles have been successfully converted into the potentially




**Scheme 5.** *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (8 mol%), $K_2CO_3$ (2 equiv.) in $H_2O$, LiCl (2 equiv.), dioxane, reflux, 2–3 h; (ii) $HCO_2^-NH_4^+$, Pd/C (10%), EtOH, reflux, 3 h, 92%; (iii) 10% aq. KOH, EtOH:THF (2:1), reflux, 2.5 h, 67%; (iv) ii on **32**, reflux, 8 h, 77%.

interesting analogs (**14**, **17**, **30**, **31**) of such biologically active natural products as grossularine-1, grossularine-2 and eudistomin U.

## Acknowledgements

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