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Synthetic approaches toward the marine alkaloid prenostodione

Jeanese C. Badenock [a,*], Jason A. Jordan [a], Gordon W. Gribble [b]

[a] Department of Biological and Chemical Sciences, University of the West Indies, Cave Hill, Barbados
[b] Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

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ABSTRACT

An efficient synthesis of the core of prenostodione (**3**) is described herein featuring the base condensation of BOC-protected indole diesters **21** and **24** with *p*-methoxybenzaldehyde (**22**) and 4-[(*t*-butyldimethylsilyl)oxy]benzaldehyde (**26**). Attempts at selective saponification of the resultant diesters yielded *iso*prenostodione (**3a**) bearing the ester functionality at the C-3 position of the indole ring.

Recently, a number of blue-green algae (cyanobacteria) have been found to possess various bioactive components,[1] some of which exhibit antibacterial,[2] antimicrobial,[3] and cytotoxic effects.[4] Additional interest in some of these pigments stems from their reported protective role against high solar radiation,[5] and their potential use as active ingredients in sunblock and sunscreen lotions. We have been interested in three such indole alkaloids namely scytonemin (**1**),[6] nostodione A (**2**),[7] and prenostodione (**3**) (Fig. 1).[8]

Of these three alkaloids, prenostodione (**3**) is of particular interest mainly in view of its presumed role in the biosynthesis of nostodione A (**2**) and scytonemin (**1**). The UV-absorbing natural product prenostodione (**3**) was isolated by Ploutno et al. in 2001 as the minor pigment from *Nostoc* sp. and determined to be the *E* isomer of the indole-3-carboxylic acid derivative.[8] The combination of acid and ester functionalities led us to first consider the introduction of the 3-carboxylic acid group in the final stages of the synthesis.[9] As such, we envisioned the installation of the *p*-hydroxyphenyl moiety using either a Wittig reaction,[10] or a suitable modification, such as the Shapiro, Schlosser, or Horner–Emmons–Wadsworth reactions (Scheme 1).[11]

Keto ester **6** was therefore generated from indole (**7**) in two steps utilizing standard C-2 lithiation chemistry.[12] Unfortunately, attempts to couple **6** with phosphorus ylide **9a** resulted in poor yields of the desired alkene (**10a**), as a 1:1 mixture of isomers (14% overall yield). Furthermore, reaction of **6** with *p*-methoxybenzyl ylide **9b** and with commercially available diethyl 4-methoxybenzyl phosphonate (**9c**) failed to yield the desired alkenes (Scheme 2). The poor stereoselectivity and the low yields of the reaction caused us to abandon this route.

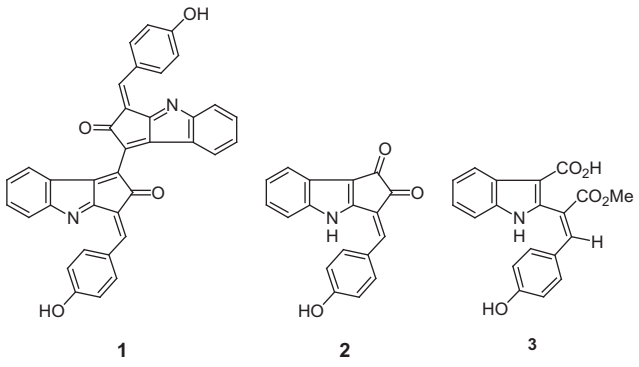
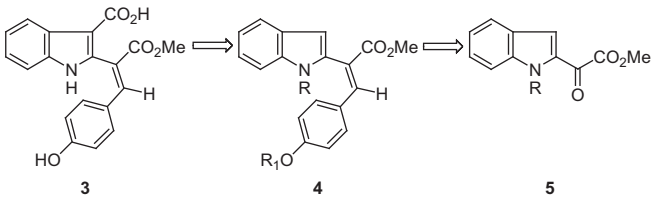


Figure 1. Cyanobacteria based indole natural products.



Scheme 1. Initial retrosynthetic approach.

* Corresponding author. Tel.: +1 246 417 4336; fax: +1 246 417 4325.
E-mail address: jeanese.badenock@cavehill.uwi.edu (J.C. Badenock).

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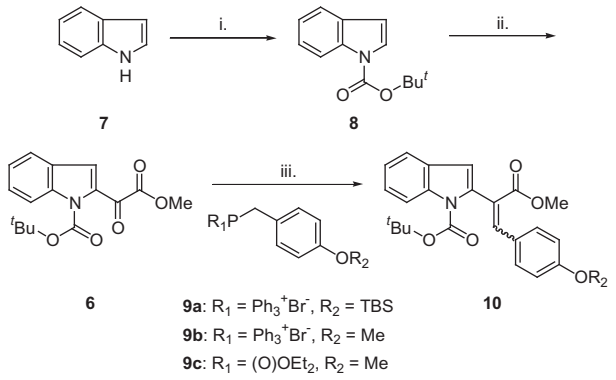
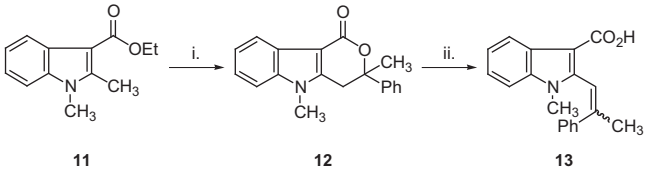


Scheme 2. Unsuccessful Wittig reaction. Reagents and conditions: (i) $((CH_3)_3CO_2C)_2O$, DMAP, THF (98%); (ii) *t*-BuLi, THF, $(CO_2Me)_2$ (71%); (iii) *n*-BuLi, **9a**, THF (14%).

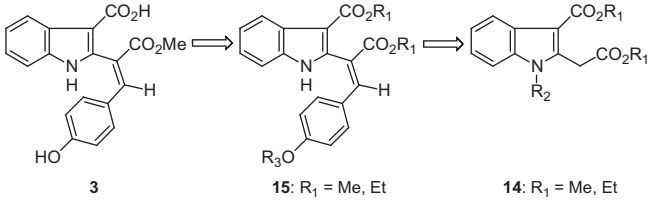


Scheme 3. Synthesis of 2-vinylindole **13**. Reagents and conditions: (i) LDA, THF, −78 °C, CH_3COPh (60%); (ii) NaH, THF (80%).

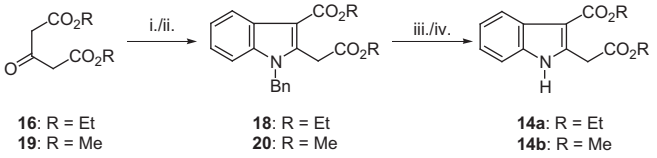
We were then drawn to a procedure by Mouaddib et al. which features a base-catalyzed condensation en route to tetrahydrobenzo[4,5]cyclohept[*b*]indol-12-one derivatives, necessary for the development of new effective chemotherapeutic agents.[13] In that work, initially elaborated by Macor et al.,[14] the vinyl group was installed by LDA-catalyzed condensation of acetophenone and 2-methylindole **11** followed by treatment with sodium hydride (Scheme 3).

Therefore, we surmised that this precedent might be useful in a biomimetic approach to prenostodione (**3**) and proposed that coupling of diester **14** with a benzaldehyde derivative could produce the desired alkene (**15**). Furthermore, this approach would eliminate the need for the installation of the C-3 acid and would only necessitate selective hydrolysis of the ester already installed at that position.[15] Indeed Bahadur et al. and others[16] utilized this chemistry with indoles and in all cases generated the desired monoesters with the acid at C-3 on the indole core. Our initial target was therefore the *N*-BOC derivatives of diesters **14** ($R_2 = CO_2Bu^t$) (Scheme 4).

While the Fischer indole reaction[17] of phenylhydrazine with diethyl acetone-1,3-dicarboxylate (**16**) in concentrated sulfuric acid gave the diethyl ester indole **14a** (R_1 = Et, and R_2 = H) in only 6% yield,[18] treatment of *N*-benzyl phenylhydrazine hydrochloride (**17**) with **16** in refluxing ethanol gave the desired indole **18**, in one step, as a white solid in 54% yield.[19] Likewise, heating **17** with dimethyl acetone-1,3-dicarboxylate (**19**) in methanol generated



Scheme 4. New retrosynthetic analysis.



Scheme 5. Synthesis of indole diesters **14**. Reagents and conditions: (i) Compound **17**, EtOH, δ (**18**: 54%); (ii) Compound **17**, MeOH, Δ (**20**: 57%); (iii) $AlCl_3$, PhH, rt, 3.5 h (**14a**: 40%); (iv) $AlCl_3$, PhH, Δ, 0.5 h (**14b**: 85%).

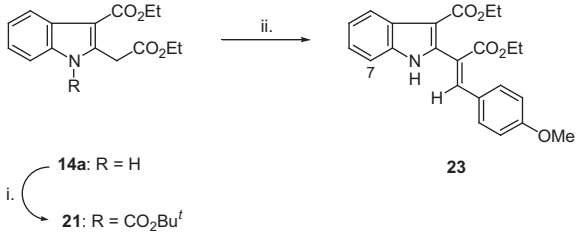
indole **20** as a white fluffy solid in 57% yield. Removal of the benzyl group seemed promising based on a number of reports describing debenzylation from indole nitrogens.[20] Gratifyingly, treatment of indole **18** with anhydrous aluminum chloride ($AlCl_3$) in anhydrous benzene at room temperature resulted in indole **14a** (R_1 = Et, and R_2 = H), albeit in only 40% yield after 3 h at room temperature.[21,22] We fared better with dimethyl indole **20**, which was converted smoothly into the parent indole **14b** (R_1 = Me, and R_2 = H), in 85% yield, with $AlCl_3$ at reflux after 30 min (Scheme 5).[23]

Reprotection of the indole nitrogen of **14a**, using di-*tert*-butyl dicarbonate and DMAP generated *t*-butoxy carbamate **21** in 85% yield.[24] The Macor-precedented condensation reaction was performed with LDA and the resulting anion was treated with commercially available *p*-methoxybenzaldehyde (**22**). Pleasingly, we obtained the coupled alkene (**23**), after stirring with sodium hydride in refluxing THF, in 54% yield. The ^1H NMR spectrum of **23** indicated a predominance of one isomer and only trace (<5%) amounts of the other (Scheme 6). From NOE experiments, we concluded that alkene **23** possesses the *Z* geometry (opposite to the natural product) based on the observation that irradiation of the indole NH singlet (δ = 8.84) showed a positive NOE enhancement of the vinyl singlet (δ = 7.88) in addition to the C-7 multiplet.

With sufficient **23** in hand, we preliminarily investigated the selective hydrolysis of the ethyl ester functionalities of this indole alkene. Using 1 N KOH in methanol, we were pleasantly surprised when after 1 h at reflux we observed the cleavage of one ethyl group in 93% yield.[16b,25] However, we have been unable to determine conclusively which ester was removed.

The results of this hydrolysis attempt and the perceived difficulty associated with the transesterification of the remaining ethyl ester to the methyl ester found in the natural product prompted us to utilize dimethyl ester **24** for the coupling. Thus, **14b** was protected as the *N*-BOC derivative (**24**) in quantitative yield, and then condensed with *p*-methoxybenzaldehyde (**22**) under identical conditions to those used with diethyl ester **21** to give the coupled alkene **25**, in an overall yield of 69% (Scheme 7). Alkene **25** contained one major isomer (16% minor isomer) determined to be the *Z*-isomer based on NOE experiments.[26]

Attempts at cleavage of the methyl ester and methyl ether in **25** were unsuccessful[27,28] but a change in the protecting group of the phenolic coupling unit, however, from the methyl ether to the



Scheme 6. Coupling of diethylindole **21** with **22**. Reagents and conditions: (i) $((CH_3)_3CO_2C)_2O$, DMAP, THF, rt (85%); (ii) LDA, THF, *p*-$OMeC_6H_4CHO$ (**22**), −78 °C; NaH, THF, Δ, 1 h (54%).