A Synthetic Approach to the Communesins

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Dedicated to Professor Jack E. Baldwin in celebration of his 70th birthday

Abstract: A synthetic approach to the communesin family of indole alkaoids has been investigated, with a cascade reaction sequence involving formation of a transient 1-alkoxycarbonylimidazole intermediate and subsequent addition onto an indole as the key step.

Key words: alkaloids, indoles, cascade reactions, heterocycles, communesins

The communesins are a family of structurally complex indole alkaloids found in marine strains of *Penicillium* sp. (Figure 1). Communesins A and B were first isolated by Numata in 1993,[1a] since when seven more congeners have been reported.[1] Communesin B is the most biologically active member of the family, exhibiting a moderate cytotoxic effect on P-388 leukemia cells with ED_{50} = 0.45 μg/mL. The heptacyclic framework of the communesins contains several synthetically challenging features, most notably two adjacent quaternary stereocentres and two aminal groups. The biosynthesis of the communesin alkaloids has been suggested to result from oxidative dimerisation of two tryptamine moieties.[2] The communesins have attracted considerable synthetic interest over the past five years, with the first synthesis of a member of the communesin family, communesin F, recently achieved by Qin.[3] Several model studies have also been undertaken.[4] The structurally related indole alkaloid perophoramidine, containing two amidine units and halogenated phenyl rings, was characterised by Ireland in 2002.[5] This natural product was synthesised by Funk,[6a] and a synthesis of dehaloperophoramidine was completed by Ranier.[6b]

An interesting approach to the core of the communesins is to instigate a hetero Diels–Alder reaction between an aza-*ortho*-xylylene[7] as the diene and an indole carbon–carbon double bond as the dienophile. This idea has been examined by Stoltz[4a] and Funk,[4b,c] but without formation of the key vicinal quaternary centres of the communesins. Our approach was to synthesise a substituted 1,3-benzoxazin-2-one **4** that could undergo a precedented[8] thermal [4+2] cycloreversion with loss of carbon dioxide to generate an aza-*ortho*-xylylene **5** that would be set up for an intramolecular [4+2] cycloaddition onto the *N*(1)-methyl indole, generating one of the aminal units and the adjacent quaternary centres in one step to give **6** (Scheme 1). Such a cascade reaction sequence would result in a rapid build up of functionality and provide a platform for synthetic endeavours towards the communesins. This scheme is a modification of an earlier biomimetic proposal for synthesis of the communesins made by Prof. J. E. Baldwin.

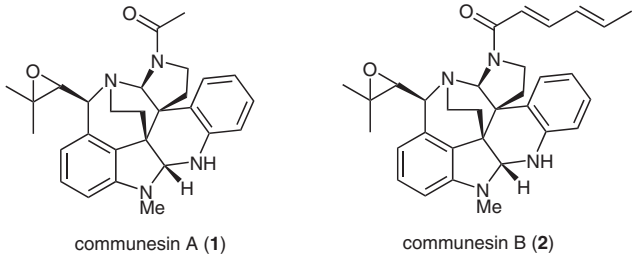
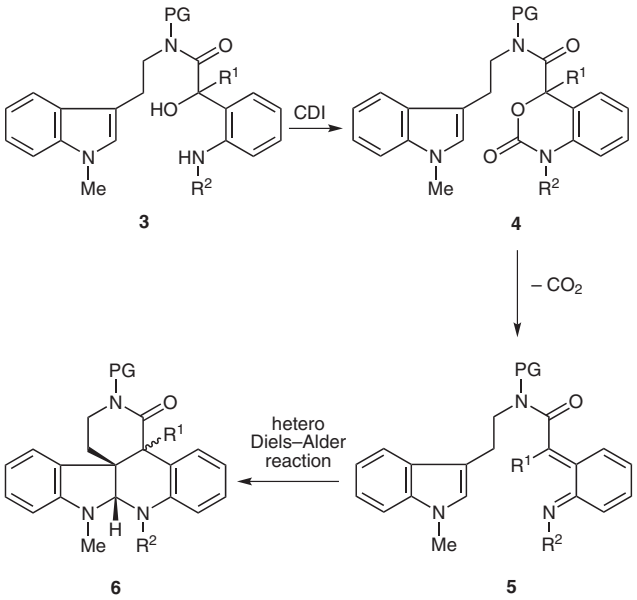


Figure 1 Communesins A and B



Scheme 1 Planned formation of the communesin core

In order to investigate this idea, tryptamine **7** was reacted with *N*-Boc-isatin in THF at room temperature to give ketone **8** (Scheme 2). Treatment of this compound with allylmagnesium bromide gave tertiary alcohol **9**, which was converted into the 1,3-benzoxazin-2-one **10** by reaction with 1,1′-carbonyldiimidazole (CDI) in THF. Removal of the *N*-Boc protecting group of **9** with TFA in CH_2Cl_2 gave amino alcohol **11**, which was reacted with CDI to give 1,3-benzoxazin-2-one **12**.

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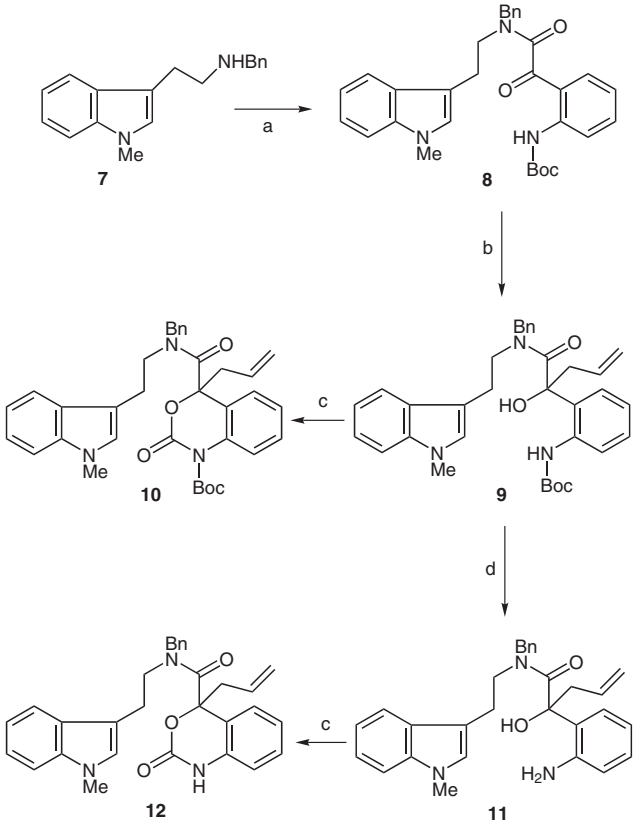
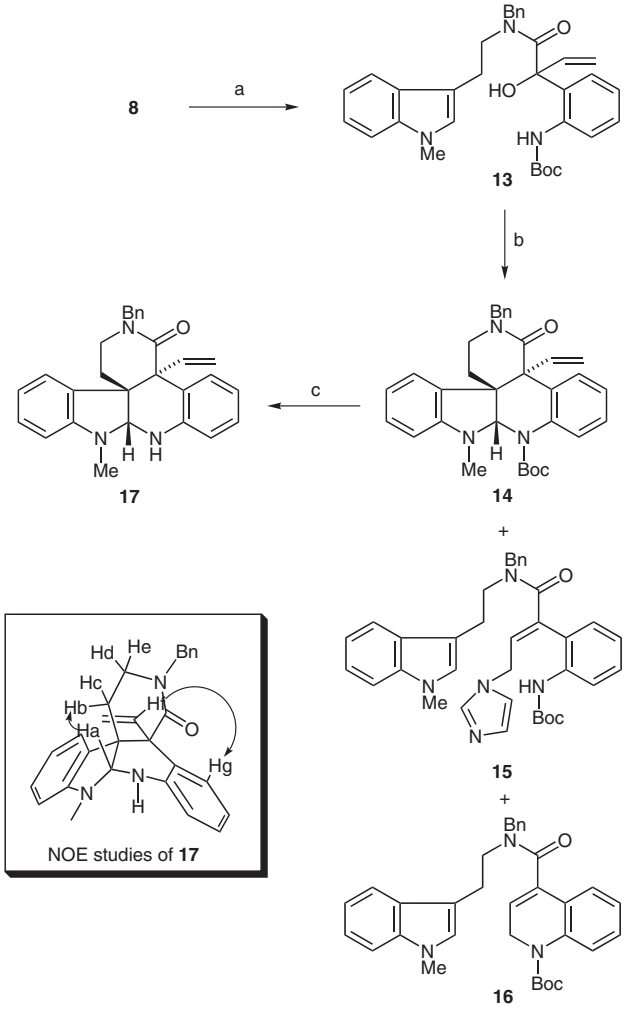


Scheme 2 *Reagents and conditions*: (a) *N*-Boc-isatin, THF, r.t., 18 h, 81%; (b) allylmagnesium bromide, THF, r.t., 2 h, 73%; (c) CDI, THF, 60 °C, 2 h, 83% (for **10**), 88% (for **12**); (d) TFA, CH_2Cl_2, r.t., 1 h, 93%.



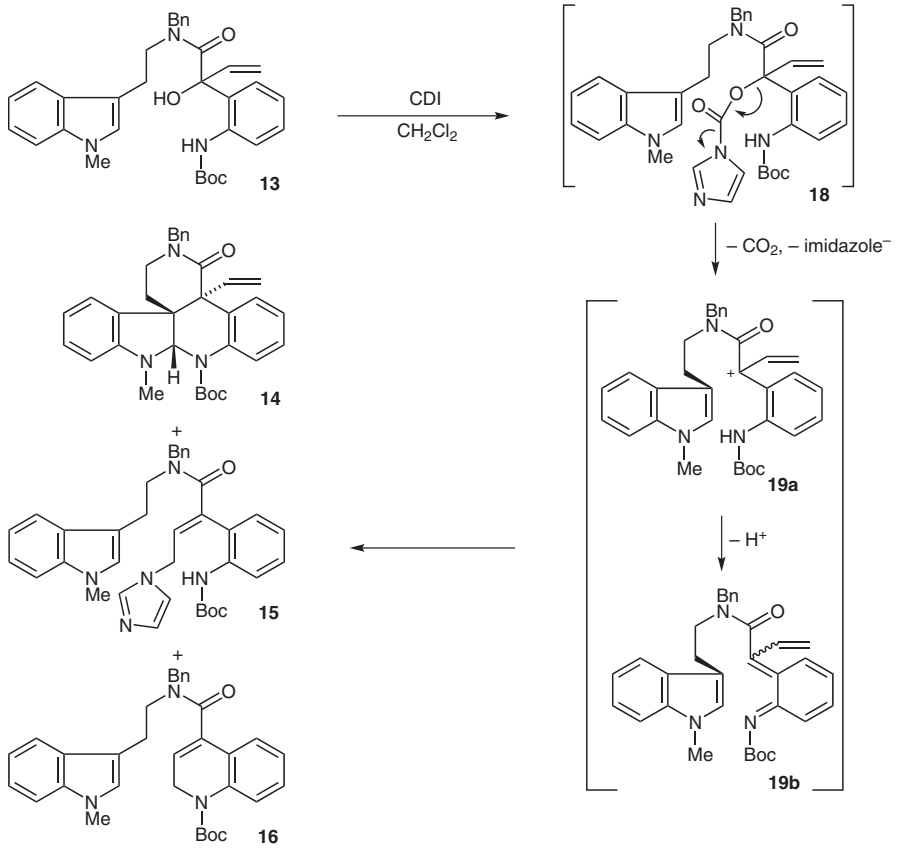
Scheme 3 *Reagents and conditions*: (a) vinylmagnesium bromide, THF, 0 °C, 1 h, warm to r.t., 1 h, 89%; (b) CDI, CH_2Cl_2, 40 °C, 48 h, 36% (**14**), 42% (**15**), 10% (**16**); (c) TFA, CH_2Cl_2, r.t., 2 h, 79%.

However, heating compounds **10** and **12** up to temperatures of 220 °C failed to generate the desired aza-*ortho*-xylylene intermediates and no hetero Diels–Alder adducts were observed, with the cyclic carbamate structures remaining intact under these conditions. Reaction of **9** with CDI at room temperature gave an isolable, but unstable in solution, 1-alkoxycarbonylimidazole with initial addition of CDI to the tertiary alcohol having occurred.

In contrast, substitution of a vinyl group for the allyl group gave very different reactivity. Reaction of amino alcohol **13** (formed by addition of vinylmagnesium bromide to ketone **8**) with CDI in CH_2Cl_2 at 40 °C gave pentacyclic aminal **14** in 36% yield, alongside allylic imidazole **15** (42%) and dihydroquinoline **17** (10%, Scheme 3). Compound **14** contains five of the seven rings of the communesins, with the vicinal quaternary centres and one of the aminal functional groups being formed in one step. The deprotected aminal group of **17** showed characteristic chemical shifts of δ = 4.59 and 82.9 ppm in the ^{1}H NMR and ^{13}C NMR spectra, respectively. The NOE studies on **17** showed strong NOE interactions between Ha and Hb/Hc and between Hf and Hg, but the absence of any NOEs between Hf and Ha/Hb or Hd/He indicated that the six-membered lactam had been formed with *syn* stereochemistry. This analysis was later confirmed by single-crystal X-ray crystallography.[9]

The products **14**–**16** can be rationalised by either of two related mechanisms as outlined in Scheme 4. Firstly, it can be considered that initial formation of the activated carbamate intermediate **18** is followed by loss of carbon dioxide and an imidazole anion to form the stabilised allylic carbocation **19a**. Intramolecular attack of the indole to the carbocation centre would give a spirocyclic indolenium ion, which could be attacked by the neighbouring NHBoc group to furnish **14**. The byproduct **15** might be formed by intermolecular attack of an imidazole anion at the CH_2 terminus of the allyl cation **19a**, while **16** could be formed via intramolecular attack by the NHBoc group at the same site. Formation of carbocationic intermediates by decarboxylation of such 1-alkoxycarbonylimidazoles has been postulated in the formation of imidazoles from primary and secondary alcohols by reaction with CDI.[10]

Alternatively, the products of the reaction can be explained by invoking a genuine aza-*ortho*-xylylene intermediate **19b**. This reactive species could undergo either [4+2] cycloaddition onto the indole C=C to give **14**, or a



Scheme 4 Proposed mechanism for CDI-mediated cyclization of indole **13**

6π-electrocyclic reaction involving the vinyl group to give dihydroquinoline **16**. Attack by imidazole onto the terminal alkene could give allylic imidazole **15**.

Although the pentacyclic compound **14** was formed in relatively modest yield, the rapid assembly of two new rings and two vicinal quaternary centres adjacent to an aminal group render it practical in terms of a synthetic approach to the communesins. The desired product **14** is significantly less polar than the byproducts and could be readily purified by flash chromatography on silica gel.

In order for *N*-benzyl lactam **14** to be elaborated towards communesin the lactam C–N bond would need to be cleaved as the relative stereochemistry of the lactam ring junction is opposite to that found in the communesins. To activate the lactam to nucleophilic attack, the benzyl group was removed under Birch reduction conditions and replaced by a tosyl group to give *N*-tosyl lactam **20** in 80% yield over two steps (Scheme 5). Reduction of this compound with $LiAlH_4$ furnished amino alcohol **21** in 95% yield, while treatment with DIBAL-H in CH_2Cl_2 gave hemiaminal **22** in 62% yield as a 1:1 mixture of epimers.

A Wittig reaction between aldehyde equivalent **22** and Ph_3P=CHOMe gave enol ether **23** in 67% yield as a single alkene stereoisomer. A coupling constant of 6.4 Hz between the newly formed vinylic protons of enol ether **23** indicated that the *Z*-isomer had been formed. It is now intended that enol ether **23** could undergo acid-catalysed hydrolysis, followed by reductive amination of the resultant aldehyde, to give a diamine **24**. Oxidative cleavage of the terminal alkene could then allow formation of the second aminal moiety to give **25** and complete the synthesis of the core structure of the communesins.

In conclusion, a short synthetic route to the core of the communesins has been developed. The key step is a CDI-mediated cascade reaction in which a proposed transient 1-alkoxycarbonylimidazole intermediate fragments to give either a stabilised allylic carbocation or an aza-*ortho*-xylylene species, which undergoes intramolecular reaction with an indole carbon–carbon double bond in either an ionic two-step or [4+2] cycloaddition process. In this manner two adjacent all-carbon quaternary centres and an aminal group are formed in one step. The product of this cascade reaction has been elaborated to a compound, which should allow synthesis of the second aminal group of the communesins in a few steps.

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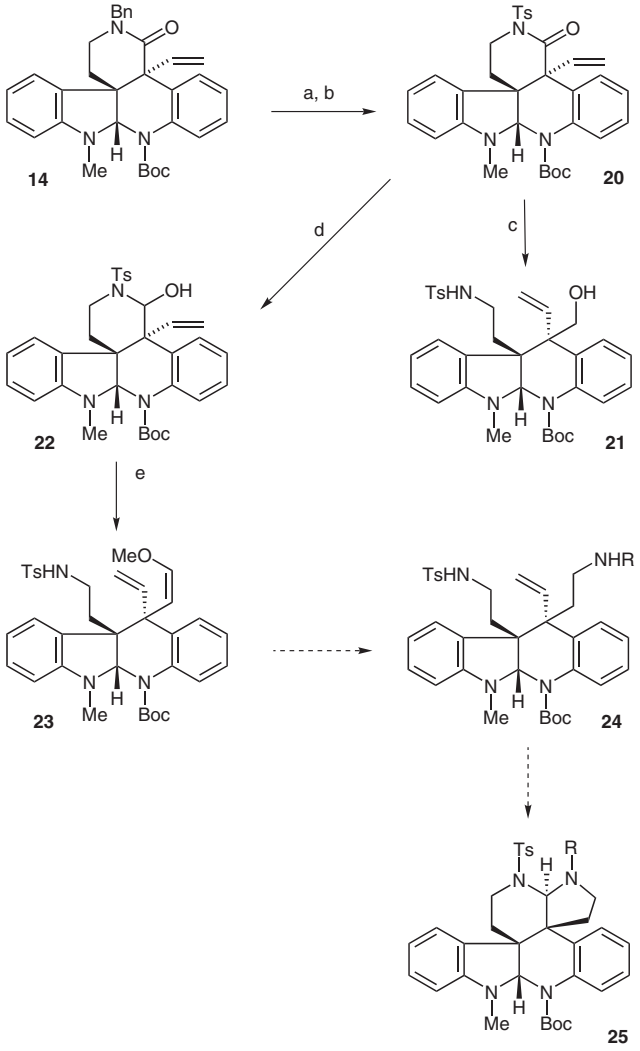

Scheme 5 *Reagents and conditions*: (a) Na, liq. NH_3, THF, –78 °C, 20 min; (b) TsCl, LHMDS, THF, 0 °C, 1 h, 80% over 2 steps; (c) $LiAlH_4$, THF, r.t., 30 min, 95%; (d) DIBAL-H, CH_2Cl_2, r.t., 30 min, 62%; (e) $Ph_3P(Cl)CH_2OMe$, NaHMDS, THF, 0 °C, 30 min, 67%.

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(9) Crystal structure obtained for compound **20**. CCDC 689636 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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