Synthetic studies and biosynthetic speculation on marine alkaloid chartelline†

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Synthetic studies and biosynthetic speculation on chartelline inspired by an unexpected reaction are described.

Chartellines A–C (Fig. 1), highly halogenated marine alkaloids isolated in the 1980s, have been recently paid rapidly increasing attention from the synthetic organic community, although significant biological activities have not been reported.[1] These alkaloids posses an extraordinary unique molecular architecture densely packed with three biologically important heterocycles: indolenine (indole derivative), β-lactam and imidazole. The conformation is also quite unique in that the indolenine moiety is stacked with the imidazole through *Z*-alkene with *gem*-dimethyl group and β-chloroenamide moiety as spacer. Recently, Baran *et al*. reported the first total synthesis of chartelline C based on their biosynthetic hypothesis,[2] and several other groups have reported their extensive synthetic work towards chartelline and its related alkaloids.[3–5] Herein, we describe our endeavor towards the synthesis of chartelline C (**3**) on the basis of our own synthetic methodology, and a biosynthetic consideration of chartelline and its related natural products, inspired from an unexpected reaction encountered during this study.

We have studied the synthesis of chartelline C according to a synthetic plan based on our own methodologies,[6] (1) β-lactam formation through nucleophilic substitution by the 3-position of indole at amide nitrogen,[6b] (2) synthesis of *N*-hydroxyenamide by *N*-acylation of oxime (Scheme 1).[6c] We envisaged that the indolenine-spiro-β-lactam could be synthesized from macrolactam **4** by a transannular variant of the β-lactam formation. The macrocyclic *N*-hydroxyenamide **4** would be constructed by the intramolecular *N*-acylation of oxime **5** as a precursor, which was retrosynthesized into an indole segment **6** and alkynylimidazole segment **7**.

2,6-Dibromoindole acetic acid methyl ester **6** as the indole segment was easily prepared from indole-3-acetic acid methyl ester by regioselective bromination[7] followed by Boc-protection.[8] On the other hand, the alkynylimidazole segment **7** was synthesized from vinyl imidazole **8** reported by Wood.[5] Dihydroxylation of the vinyl group was followed by protection of the diol as an acetonide to give **9** in good overall yield (Scheme 2). The benzyl group was deprotected under hydrogenolysis, and the ester group within compound **10** was then converted to acetylene **7** in three steps, including reduction of the ester with $LiAlH_4$, oxidation with IBX and alkynylation of the resulting aldehyde with Ohira–Bestmann's reagent.[9] With the two segments in hand, we examined the coupling reaction between **6** and **7**.

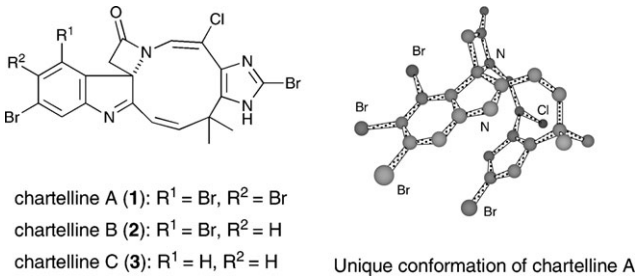
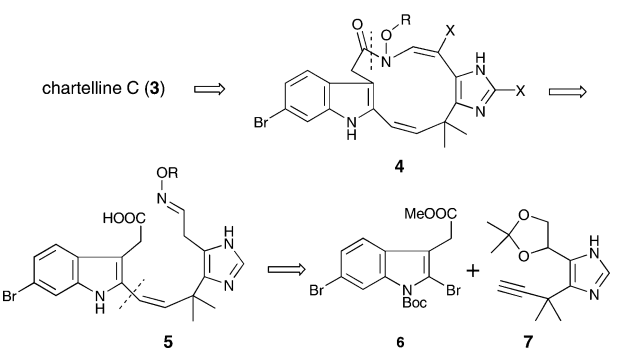


Fig. 1 The structure of chartellines A–C and the conformation of chartelline A.

One issue to consider in this coupling was the regioselectivity between the two bromo-substituents within indole segment **6**. Taking into account several precedented examples of regioselective palladium catalyzed cross-coupling of dihalogenated heteroaromatics,[10] we anticipated the bromide at the 2-position of the indole would be more reactive than at the C-6 position in the Sonogashira reaction.[11] To our delight, the coupling between acetylene **7** and dibromoindole **6** took place in the presence of $Pd_2(dba)_3$–PPh_3 and CuI as catalyst under carefully degassed conditions to afford the desired coupling product **11** as a single regioisomer (Scheme 3).[12] It is worthwhile noting that neither the other regioisomer nor the doubly alkynylated indole was detected under these conditions.

Reduction of the sterically hindered acetylene within **12** to the corresponding (*Z*)-olefin in the presence of 6-bromoindole proved to be very difficult. Numerous experiments led us to find that acetylene **12** prepared from **11**[13] was successfully reduced with Zn–Cu[14] in the presence of hydrochloric acid to give (*Z*)-alkene **13** in good overall yield.[15] It is noteworthy that



Scheme 1 Synthetic plan for chartelline C.

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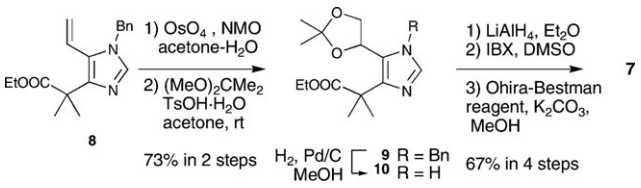
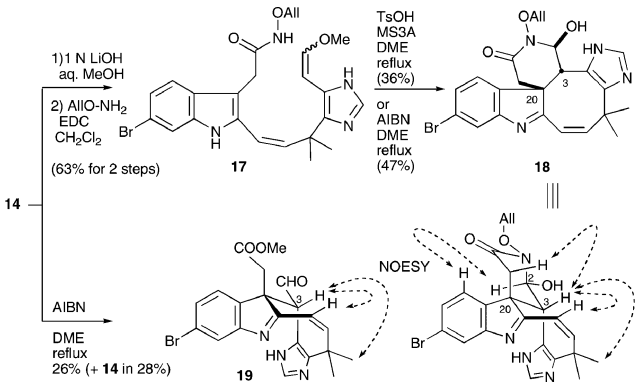


Scheme 2 Synthesis of imidazole segment **7**.

the bromo substituent in indole **12** was intact even when an excess of Zn–Cu was used in this reaction. The acetonide group was hydrolyzed and then cleaved with sodium periodate to give the corresponding aldehyde, which was homologated by the use of a Wittig reaction, thus providing vinyl ether **14**. The methyl ester of **14** was hydrolyzed with lithium hydroxide, and the vinyl ether was hydrolyzed under acidic conditions in the presence of *O*-allylhydroxylamine to furnish oxime **15**, which was set up for the macrolactamization. Compound **15** was transformed to acid chloride **16**[16] through silylation of the carboxylic acid, benzoylation of the imidazole and chlorination with oxalyl chloride[17] and then exposed to the cyclization conditions. However, extensive examination of the reaction proved the desired cyclization of **16** to be difficult.[18]

At this conjuncture, we turned to an alternative for the construction of *N*-hydroxymacrolactam **4** by utilizing an intramolecular condensation of *O*-allylhydroxamic acid with aldehyde, which could be prepared from vinyl ether **14** (Scheme 4). Thus, the ester of **14** was transformed into *O*-allylhydroxamate **17** in two steps including alkaline hydrolysis followed by condensation with *O*-allylhydroxylamine. Upon refluxing **17** with *p*-toluenesulfonic acid and MS3A in DME, the desired enamide product was not obtained, but instead a pentacyclic indolenine **18** was obtained in 36% yield. The structure was determined by NMR and MS experiments as depicted in Scheme 4; connection between the C-3 and C-20 was elucidated by the HMBC spectrum, NOESY correlations support the depicted stereochemistry, and a large coupling constant (J_{2-3} = 9 Hz) indicates a *trans*-diaxial relationship between these protons.

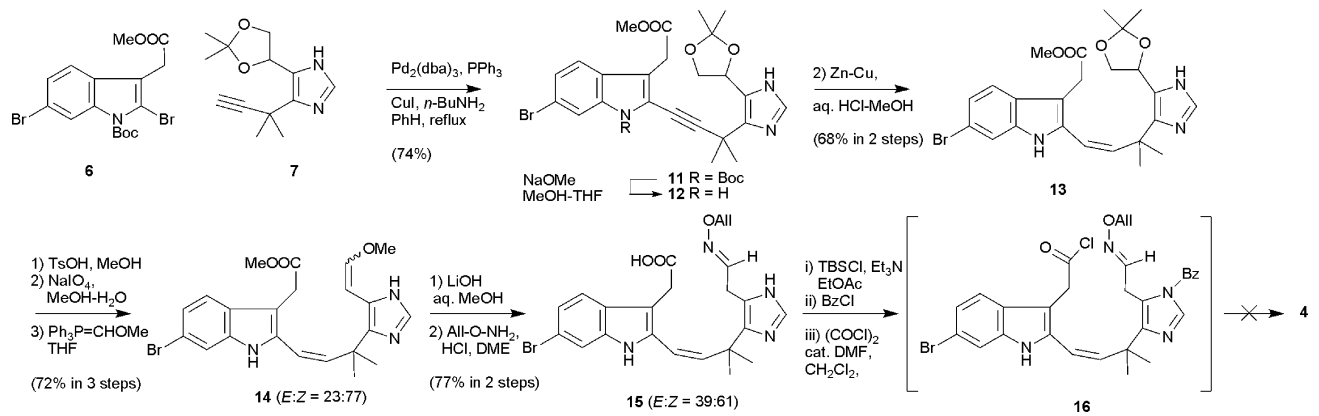
Despite extensive examination, we could not find the conditions to give the desired macrolactam **4** (X = H, R = CH_2–CH=CH_2). However, during these experiments, we noticed several crucial factors influencing the production of **18**; the reaction did not proceed under argon atmosphere and



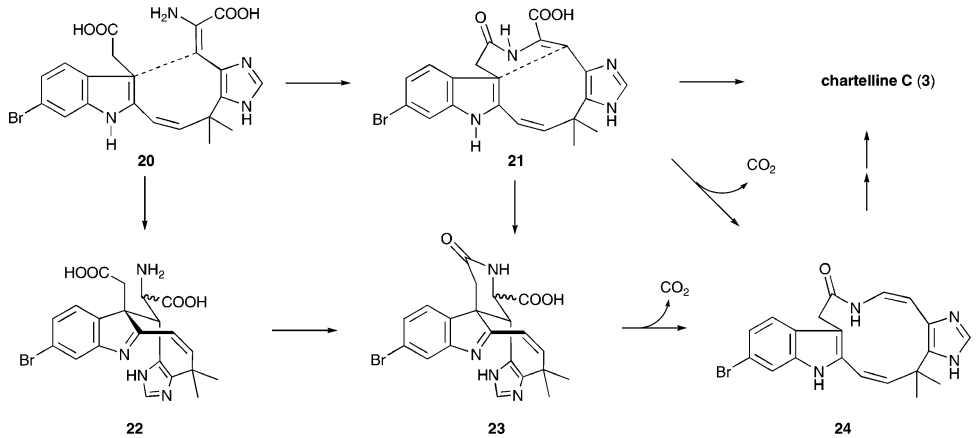
Scheme 4 Attempted cyclization.

acid was not necessary for the formation of **18**. These results strongly suggest a radical mechanism for the reaction, though the detail is still not clear. Although the desired product **4** has not been obtained, we envisioned that the unexpected product **18** might be a precursor for a macrolactam such as **4** (*vide infra*). Further experiments led us to find that pentacyclic product **18** was best obtained by refluxing **18** with AIBN in DME (47% yield). Since a similar compound, namely indole **14** cyclized to give tetracyclic indolenine **19**[19] under the optimized conditions, it indicates that **18** is formed through ring closure of the eight-membered ring followed by formation of the six-membered aminal. The facile formation of the eight-membered ring is probably due to the *Z*-alkene linker with geminal dimethyl group, which may fix the stacking between the imidazole and indole rings to approximate the C-3 position to the C-20 position (Scheme 5).

The finding of the unexpected reactions inspired us to speculate an alternate biosynthetic pathway for the 12-membered macrolactam **24** from **20** as a precursor not through **21** (Scheme 5).[20] Formation of an eight-membered intermediate **22** from **20** is followed by six-membered amide formation to give rise to pentacyclic product **23**, which undergoes decarboxylative fragmentation to macrolactam **24**. The other biogenesis through the 12-membered lactam **21** is also possible; intramolecular condensation of **20** would give compound **21**, which undergoes a transannular reaction resulting in the formation of the pentacyclic compound **23**. These proposed biosynthetic pathways are also attractive as an alternative



Scheme 3 Synthesis of oxime for the cyclization.



Scheme 5 Proposed biosynthetic pathways.

synthetic route for **24**. Further synthetic studies along this line are being pursued in this laboratory.

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18. The conditions developed for *N*-acylation of oxime were employed for attempted cyclization of **16**. See ref. 6*c*.
19. The stereochemistry of **19** was determined by the NOESY correlations between H-3 and olefinic proton, and H-3 and one of the *gem*-methyl groups, as shown in Scheme 4.
20. For biosynthetic considerations, see refs. 2 and 4.