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Total Synthesis of (±)-Chartelline C

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The chartellines are a small family of marine-derived, architecturally unique alkaloids that have remained unsolved synthetic puzzles since their isolation by Christophersen and co-workers over two decades ago.[1,2] Chartelline C (**1**, Scheme 1), the family's scarcest member (~4:6:90 **1**/**3**/**2** mass isolated), is composed of indolenine, imidazole, and β-lactam heterocycles arrayed in a dense, π-stacking framework that poses numerous challenges for its synthesis. In 2005, we put forth a hypothesis, supported by the empirical findings of a model study, for the origin of the chartellines in nature.[3] In this Communication, a biosynthetically inspired and strategically designed synthesis of **1** is reported, which addresses the remaining challenges of chemoselectivity and connectivity in a concise way.

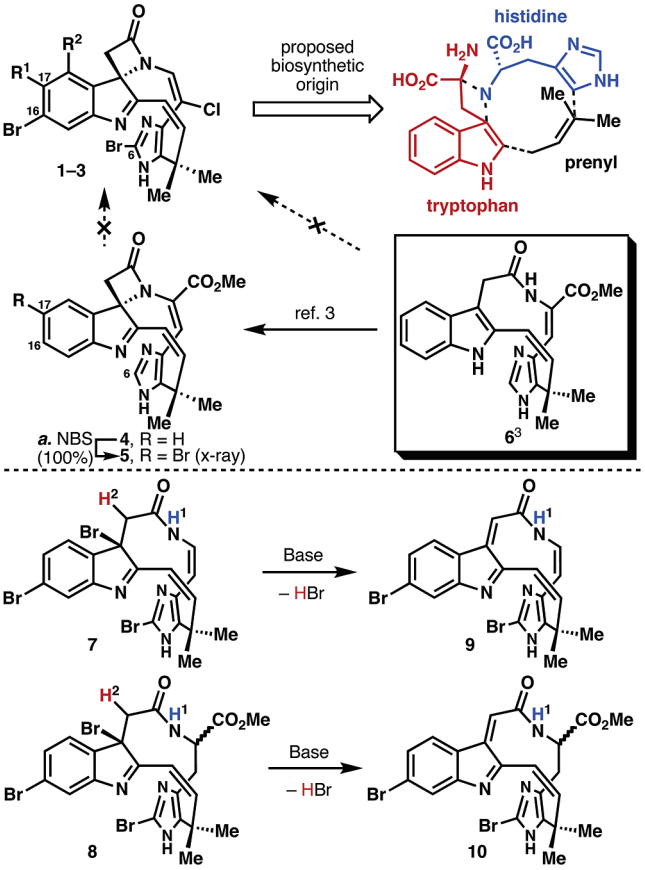
Since our initial report,[3] several unanticipated events conspired to delay the total synthesis of **1**; the most informative of these impasses are briefly summarized in Scheme 1. For instance, indole **4** favors bromination of C17 (**4** → **5**) over both C16 and C6, where bromine atoms are conserved throughout the chartellines. Furthermore, despite the ease with which model compound **6** undergoes ring contraction (**6** → **4**), the seemingly minor changes introduced into intermediates **7** and **8** prevent a similar rearrangement from taking place. Instead, facile elimination leads to acrylamides **9** and **10**, presumably because of an increase in the pK_a of N-bound proton H1 relative to the similarly acidic α-proton H2 (vide infra for mechanistic details). Consequently, a very specific sequence of events was choreographed to alter or install the requisite functionality of the chartellines: the successfully revised route to chartelline C is illustrated in Scheme 2.

The synthesis commences with a site-selective Heck−Sonogashira[4] coupling between the doubly halogenated indole **11**[6] (see Supporting Information) and the previously reported alkyne **12**[3,5] to yield 85% of indole−imidazole **13**. After extensive screening, the alkyne could be chemoselectively reduced in 80% yield using Raney nickel and then converted into the key macrocycle **17** by the following sequence:[3] (a) TBAF-mediated deprotection, (b) MnO_2 benzylic oxidation to aldehyde **14** (60% over two steps), (c) saponification, (d) BOPCl coupling with amine **15** (89% over two steps), and (e) intramolecular Horner−Wadsworth−Emmons reaction (56%) to furnish macrocycle **17** in 24% overall yield from **13**.

At this point, macrocycle **17** could be chemoselectively halogenated with bromine (in the presence of $CaCO_3$) at the β-position of the carboxyenamide. After filtration of $CaCO_3$, the action of *N*-bromoacetamide delivered the corresponding bromoenamide−bromoimidazole **18** (albeit in low conversion), along with recovered dibrominated material. With **18** in hand, the tasks of Boc-deprotection, β-lactam formation, and bromine−chlorine exchange could be accomplished in a single flask. Thus, thermolysis of **18** at 185 °C delivered in nearly quantitative yield the corresponding free indole, which was cooled to ambient temperature and treated with NBS in the presence of molecular sieves to give an unstable intermediate, tentatively assigned as tetrabromide **19**. Addition of 18-crown-6 and K_2CO_3 to the reaction mixture provided the tribromo-β-lactam **21**, which upon aqueous workup with brine underwent efficient halogen exchange at the vinylogous bromoformate to afford the desired β-chloro-carboxyenamide **22**.

Deprotection of the TMSE ester with TFA[7] smoothly delivered carboxylic acid **23**. Unfortunately, all attempts to remove this vinyl carboxylate using standard $Cu^{I/II}$ catalysis failed to deliver the natural product, owing mainly to the propensity of chloroenamide **23**

Scheme 1. Postuated Biosynthetic Origins of the Chartelline Alkaloids [Chartelline C (1): R^1 = H, R^2 = H; Chartelline A (2): R^1 = Br, R^2 = Br; Chartelline B (3): R^1 = H, R^2 = Br] and Some Informative Dead-Ends

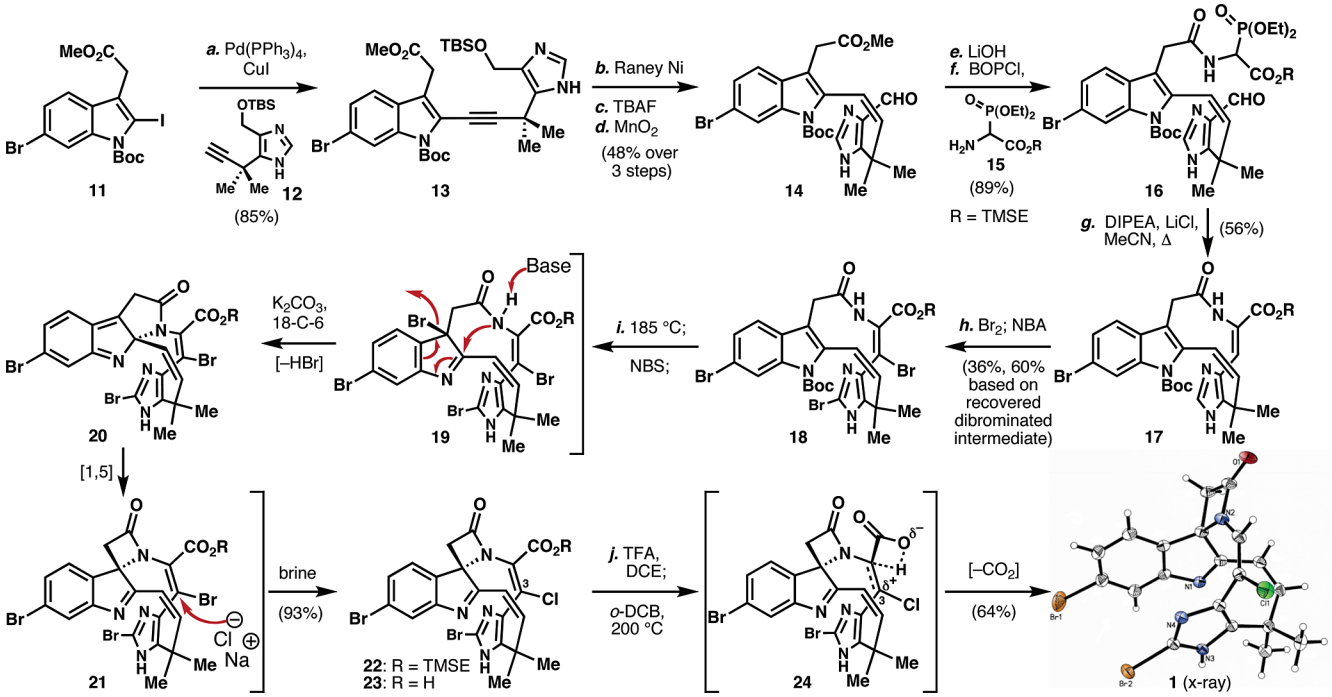


(or **1**[1b]) to undergo rapid nucleophilic substitution at C3 with either solvent or Cu-ligands. However, mass spectrometric analysis of **23** hinted at the possible thermal lability of the pendant carboxylic acid: a strong fragment peak indicated its departure. Indeed, simple thermolysis of **23** in inert reaction solvent delivered (in 64% isolated yield) **1**, whose spectroscopic values were identical to those reported in the literature for natural chartelline C.[8] Subtle electronic features are suspected to be responsible for these surprisingly mild decarboxylation conditions, namely, stabilization by chlorine lone pairs of the developing positive charge at C3 of **24**.[9] Indeed, thermal decarboxylation was not possible with substrates lacking the vinyl chloride.

The crucial transformation (**18** → **22**) warrants some added commentary. During our model study, hydroxy-pyrroloindoline **26** (Scheme 3) was consistently isolated in minor amounts (5−10%), suggesting that a complex mechanism is operative. The intermediacy of dearomatized 2*H*-indoles[10] **25** and **20** explains the C20−OH byproduct **26** and the driving-force required to form the strained β-lactam rings **21** and **4**.[10,11] On the basis of these findings, the dearomatization of a 3-halo-indolenine to a 2*H*-indole is also believed to be operative in the proposed biosynthesis of welwitindolinone A from fischerindole I.[12]

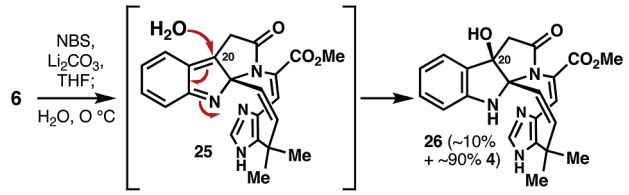
10.1021/ja0659673 CCC: $33.50

Scheme 2. Total Synthesis of (±)-Chartelline C[a]



[a] Reagents and conditions: (a) **12** (0.9 equiv), CuI (0.2 equiv), $Pd(PPh_3)_4$ (0.1 equiv), DME/Et_3N (1:1), 50 °C, 7 h, 85%; (b) Raney Ni, MeOH, 20 °C, 5 h, 80%; (c) TBAF (1.1 equiv), THF, 20 °C, 4 h; (d) MnO_2 (20 equiv), CH_2Cl_2, 20 °C, 8 h, 60% overall; (e) LiOH·H_2O (3 equiv), THF/H_2O 4:1, 20 °C, 3.5 h; (f) **15** (2.6 equiv), BOPCl (1.5 equiv), DIPEA (2 equiv), CH_2Cl_2, 0 °C, 9 h, 89% overall; (g) LiCl (10 equiv), DIPEA (20 equiv), MeCN, 70 °C, 6 h, 56%; (h) Br_2, (1.0 equiv), $CaCO_3$ (20 equiv), PhH, 20 °C, 6 h; then NBA (1 equiv), PhH, 20 °C, 12 h, 36%, 60% (see above); (i) 185 °C, 1.5 min (× 4); MeCN, 3 Å m.s., NBS (1 equiv), 20 °C; then 18-C-6, K_2CO_3, 20 °C, 1 h; then $NaHCO_3$ (sat. aq), then brine, 15 min, 93% (j) TFA/DCE 1:1, 20 °C, 4 h; o-DCB, 200 °C, 5 min, 64%.

Scheme 3. C-20 Hydroxy-Pyrroloindoline Formed During the Rearrangement of **6** → **4**



The longstanding synthetic challenge posed by the chartelline alkaloids has been answered for the first time by a short route influenced by a logical biosynthetic rationale. The idiosyncratic facility with which certain steps proceed (e.g. **18** → **22**, **23** → **1**) points to possible intermediates in a chartelline biosynthesis. Highlights of this 10 step (from **11**) synthesis include (1) chemo- and position-selective installation of the heteroaromatic halogens, (2) halogen-sparing monoreduction of alkyne **13**, (3) a simple strategy for placement of the sensitive β-chloroenamide, (4) unusually facile thermolysis of a vinyl carboxylic acid, and (5) a powerful ring contraction (**18** → **22**) whose potential utility in heterocyclic chemistry merits further investigation.

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Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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