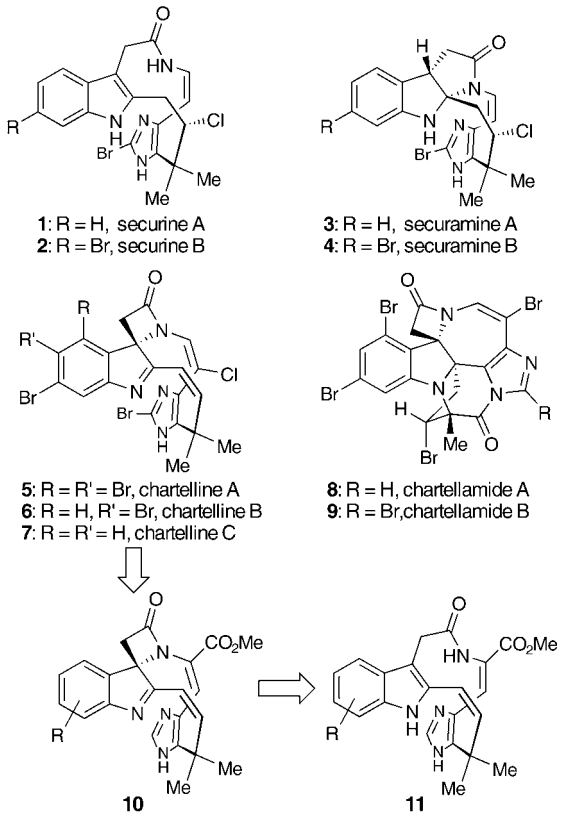

Scheme 1. Structures of the chartellines, chartellamides, securines, and securamines, and the retrosynthetic analysis of the carbocyclic skeleton.

Natural Product Synthesis

A Remarkable Ring Contraction En Route to the Chartelline Alkaloids**

Phil S. Baran, Ryan A. Shenvi, and Christos A. Mitsos*

Marine fauna continually produce molecules endowed with potent bioactivities and extraordinary structures.[1] The securines (**1**, **2**), securamines (**3**, **4**), chartellines (**5**–**7**), and chartellamides (**8**, **9**; Scheme 1) are members of a structurally unique class of natural products that were isolated by Christophersen and co-workers from the bryozoa *Chartella papyracea* and *Securiflustra securifrons*.[2] They contain an interesting arrangement of various heterocyclic entities that are wound around a prenyl unit and adorned with halogen atoms. With such a dense array of sensitive and exotic functionalities, such as spiro-β-lactam, indolenine, chloroenamide, and 2-bromoimidazole units, it is understandable why no member of this family has yet succumbed to total synthesis since their isolation over two decades ago.[3]

The belief that macrocyclic constructs such as **10** and **11** would behave differently than their individual heterocyclic subunits was central to our synthetic plan. Specifically, late-stage chemo- and regioselective halogenations and a bromine-induced rearrangement of **11** to **10** were planned. The presence of extensive halogen substitution in these natural products perhaps suggests that many of the biotransformations that create such complex polycyclic structures are indeed accomplished with electrophilic sources of bromine and chlorine; it is this hypothesis that inspired the current approach. However, there are no examples for such a ring contraction of a pyrroloindoline unit and ample precedent that suggests its failure (Scheme 2).[4] Pyrroloindoline intermediates of type **A** have not been known to undergo ring contraction to strained spiro systems of type **B** (see Scheme 2). Furthermore, an indolenine, such as **C**, can be rapidly hydrated (**D**) and undergo a 1,2-shift to an oxindole (**E**).[5] Notwithstanding this bleak outlook, we hypothesized that π stacking and conformational effects in the macrocycle **11** would provide sufficient driving force for a bromine-induced ring contraction to yield **10** (via an intermediate of type **A**). Herein, we present the successful execution of this approach, which resulted in a short and practical route to the

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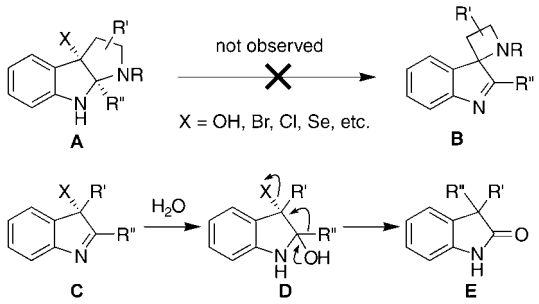
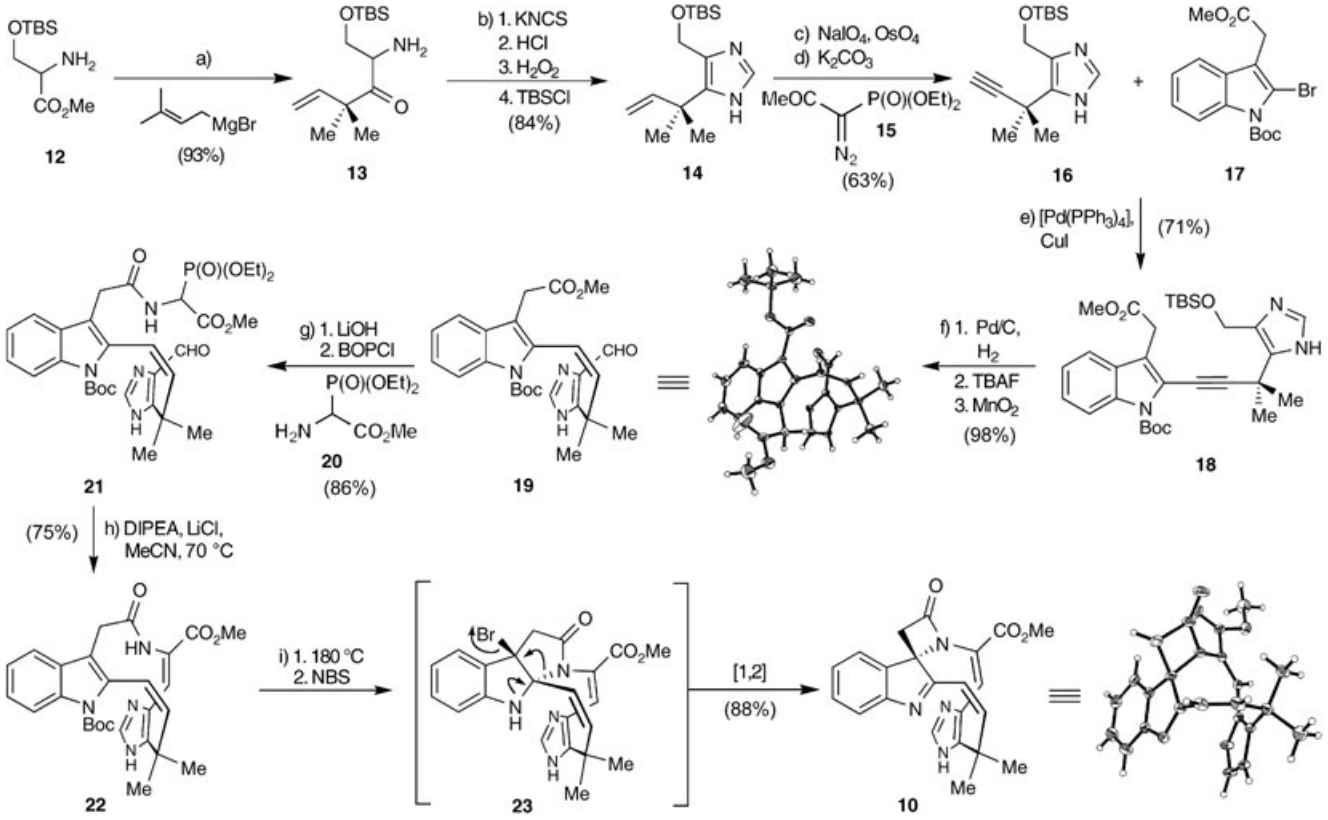


Scheme 2. The known reactivity profile of oxidized indoles suggests that the proposed rearrangement (**11**→**10**) is unlikely to occur.

carbocyclic skeleton of the chartelline, securine, and securamine alkaloid families.

The synthetic pathway to **10** is outlined in Scheme 3. Thus, treatment of the readily available serine-derivative **12** with prenylmagnesium bromide furnished α-amino ketone **13** which could be easily transformed into imidazole **14** in 84% yield via an imidazoline-2-thione intermediate.[6] The corresponding primary alcohol of **14** has been previously synthesized in nine steps[7] and was used in the total synthesis of the anticancer agents phenylahistin and aurantiamine and libraries that were based upon these compounds.[7,8] In preparation for linking the imidazole and indole subunits, it was necessary to convert the vinyl group of **14** into an alkynyl group. This conversion was carried out by the Johnson–Lemieux oxidation of **14** to the corresponding aldehyde followed by treatment with reagent **15**, developed by Ohira and Bestmann and co-workers,[9] to furnish alkyne **16** in 63% yield. The coupling of **16** and 2-bromoindole **17**[10] was accomplished by employing the method of Sonogashira et al. for a copper-accelerated[11] Heck alkyne synthesis[12] to afford **18** in 71% yield. Subsequent hydrogenation to the *cis* olefin,[13] removal of the TBS protecting group, and MnO_2-mediated oxidation of the resulting alcohol led to the crystalline aldehyde **19** (m.p. 50–55 °C, CH_2Cl_2/hexanes), whose markedly folded structure was discerned through X-ray crystallography (see Scheme 3 for the ORTEP representation). After a number of abortive attempts, the reliable Horner–Wadsworth–Emmons reaction finally emerged as an effective means to mediate the macro-

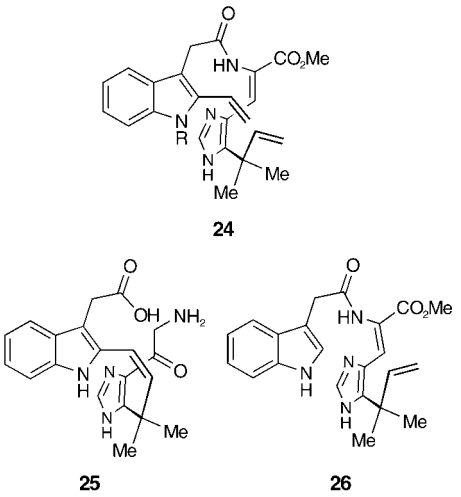


Scheme 3. Construction of the complete chartelline, securine, and securamine carbocyclic skeletons. Reagents and conditions: a) prenylmagnesium bromide, THF, −78 °C, 93%; b) 1. KNCS (20 equiv), NH_4Cl (20 equiv), toluene 105–110 °C, 4 h; 2. 6 N HCl, 25 °C, 20 min; 3. i. H_2O_2 (11 equiv), THF, 25 °C, 6 h; ii. 2 M NaOH/saturated aq $NaHCO_3$ (4:1), 25 °C, 1 h; 4. TBSCl (1.0 equiv), Et_3N (1.0 equiv), CH_2Cl_2, 25 °C, 84% from **13**; c) $NaIO_4$ (3.0 equiv), OsO_4 (0.03 equiv), THF/H_2O (2:1), 25 °C, 18 h; d) **15** (1 equiv), K_2CO_3 (1.5 equiv), MeOH, 25 °C, 6 h, 63% from **14**; e) $[Pd(PPh_3)_4]$ (0.3 equiv), CuI (0.7 equiv), *i*$PrNH_2$ (10 equiv), DME, 70 °C, 30 min, 71%; f) 1. H_2, 10% Pd/C (0.1 equiv), $MgSO_4$ (2 equiv), EtOH, 25 °C, 4 h; 2. TBAF (1.1 equiv), THF, 0→25 °C, 3 h; 3. MnO_2 (20 equiv), CH_2Cl_2, 25 °C, 8 h, 98% from **18**; g) 1. LiOH (3 equiv), THF/H_2O (4:1), 25 °C, 5 h; 2. **20** (2.6 equiv), BOPCl (1.5 equiv), DIPEA (2.0 equiv), 0 °C, 2 h, 86% from **19**; h) LiCl (9.0 equiv), DIPEA (20 equiv), CH_3CN, 70 °C, 4 h, 75%; i) 1. 180 °C, 8 min; 2. NBS (1.0 equiv), $KHCO_3$ (20 equiv), THF/H_2O, 35 min, 88% from **22**. TBS = *tert*-butyldimethylsilyl , KNCS = potassium thiocyanate, Boc = *tert*-butoxycarbonyl, DME = 1,2-dimethoxyethane, TBAF = tetra butylammonium fluoride, BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, DIPEA = diisopropylethylamine, NBS = *N*-bromosuccinimide.

cyclization.[14] Aldehyde **19** was primed for this reaction through saponification with LiOH and coupling with amine **20**[15] in the presence of BOPCl to furnish phosphonate **21** in 86% yield. Macrocyclization under the conditions developed by Masamune, Roush, and co-workers[16] produced macrocycle **22** in 75% yield and set the stage for the critical rearrangement.

Macrocycle **22** was converted into the chartelline skeleton **10** in 88% yield and in a single operation by simple thermolytic removal of the Boc protecting group in **22** (180°C, no solvent)[17] followed by treatment of the resulting free indole (**11**, Scheme 1) with NBS and aqueous $KHCO_3$. The structure of this crystalline substance (m.p. 190–220°C (decomp; CH_3CN)) was verified by X-ray crystallographic analysis (see Scheme 3 for the ORTEP representation). Although we speculate that the reaction proceeds through intermediate **23**, several degenerate pathways to **10** could also be envisaged.

As alluded to above, a number of unanticipated roadblocks were encountered during our efforts to accomplish macrocyclization. Some of these experiences are briefly summarized in Scheme 4, with the resistance of **24** to undergo ring-closing metathesis, the failure of a seemingly simple macrolactamization (**25**), and the refusal of **26** to take part in a Heck-type[18] ring closure.



Scheme 4. Selected dead-end routes to the chartelline, securamine, and securine carbocyclic skeletons.

Notable aspects of the approach described herein include synthetic efficacy (approximately 19% overall yield and 10 steps); rapid access to the carbocyclic skeletons of the chartelline, securine, and securamine alkaloids; and a remarkable ring contraction (**22**→**10**) that proceeds in high yield, despite the inherent ring strain of the β-lactam unit and an abundance of discouraging literature precedent (Scheme 2). The distinctive architecture of the chartelline alkaloids inspired this approach, and it is possible that a similar strategy is employed in nature to forge the intriguing spiro-β-lactam ring in the chartellines from securine-like structures. Completion of the total synthesis of the chartellines and related alkaloids will be reported shortly.[19]

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