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Natural Products

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Synthetic Studies on Chartelline C: Stereoselective Construction of the Core Skeleton**

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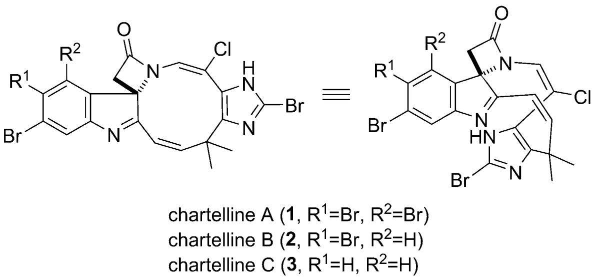
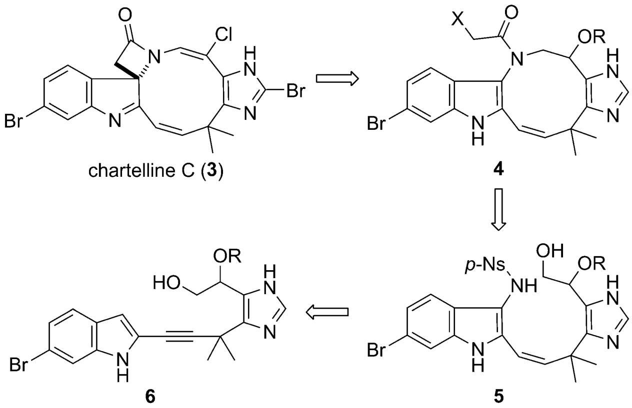
The chartellines (**1**–**3**; Scheme 1) were isolated from the marine bryozoan *Chartella papyracea* in the 1980s by Christophersen and co-workers.[1] The core structure of the chartellines includes a β-lactam, an indolenine, and 2-bromoimidazole. In addition, these natural products have a unique rigid, folded conformation resulting from π–π stacking between the indolenine and imidazole. To date, Baran et al. have reported the only a racemic total synthesis of chartelline C,[2] and several other groups have reported synthetic approaches to the chartellines.[3–6] Herein, we disclose a stereoselective construction of the core skeleton of chartelline C.

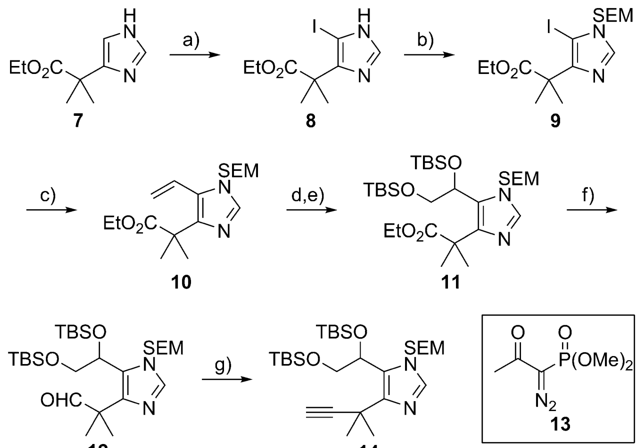


Scheme 1. Structure of chartellines.

Our retrosynthetic analysis is shown in Scheme 2. We envisioned that the enamide moiety in **3** would be constructed by elimination of a hydroxy group at the position β to the lactam nitrogen on the ten-membered ring. Formation of the β-lactam would be performed by a stereoselective alkylation at the 3-position of the indole, with the stereochemistry controlled by the conformation of the ten-membered ring in intermediate **4**. The conformation would be affected by the secondary hydroxy group on the ten-membered ring. The ten-membered ring in **4** would be synthesized by an intramolecular Mitsunobu reaction of nosyl amide **5**,[7] which could be derived from **6** by introduction of a nitrogen atom at the 3-position of the indole through a diazo coupling reaction,[8]



Scheme 2. Retrosynthesis. Ns = nitrobenzenesulfonyl.



Scheme 3. a) NIS, $ClCH_2CH_2Cl$, RT; Na_2SO_3, $EtOH/H_2O$ (3:1), reflux; b) SEMCl, $i Pr_2NEt$, TBAI, THF/$ClCH_2CH_2Cl$ (1:1), reflux, 94% (2 steps); c) tri-*n*-butyl(vinyl)tin, $[Pd(PPh_3)_4]$, *o*-xylene, reflux, 97%; d) OsO_4, NMO, acetone/H_2O (1:1), RT, 93%; e) TBSOTf, $i Pr_2NEt$, CH_2Cl_2, 0 °C, 95%; f) DIBAL, CH_2Cl_2, −78 °C; g) **13**, K_2CO_3, MeOH, RT, 96% (2 steps). DIBAL = diisobutylaluminum hydride, NIS = *N*-iodosuccinimide , NMO = *N*-methylmorpholine *N*-oxide, SEM = 2-(trimethylsilyl)ethoxymethyl, TBAI = tetra-*n*-butylammonium iodide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

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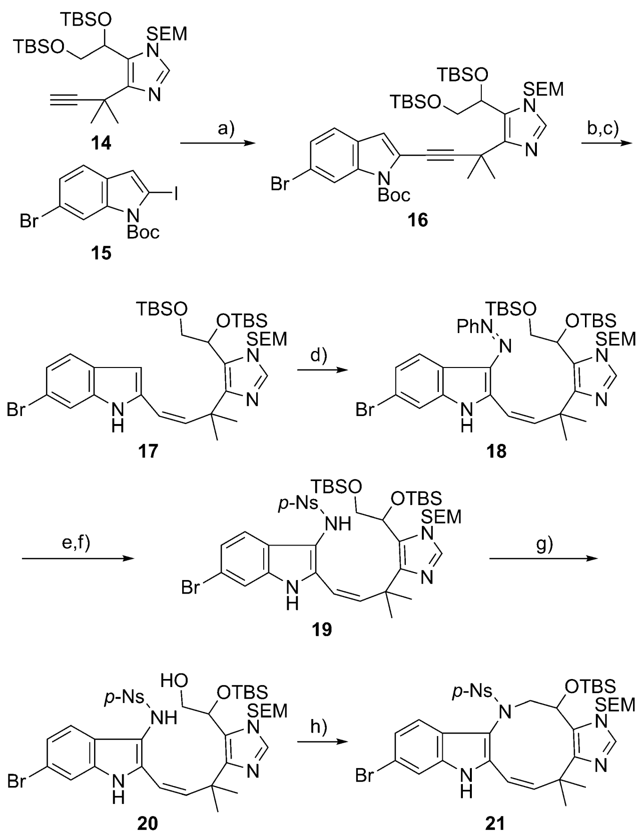
and partial reduction of the alkyne moiety. The key 2-alkynylindole **6** could in turn be synthesized by a Sonogashira coupling reaction.

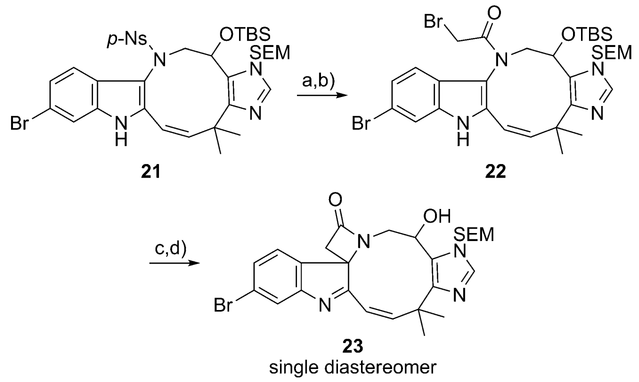
Our synthesis commenced with preparation of an imidazole unit bearing an alkyne moiety (**14**; Scheme 3). Diiodination of known imidazole **7**[9] with NIS followed by regioselective deiodination with sodium sulfite[10] led to formation of 5-iodoimidazole **8** in good yield. After protection of the imidazole with an SEM group,[11] the resultant iodide **9** was coupled with tributyl(vinyl)tin under standard Stille cross-coupling conditions to afford vinyl imidazole **10**. A subsequent osmium-mediated dihydroxylation provided a diol, which was protected with TBS groups to give bis(TBS ether) **11**. Reduction of **11** with DIBAL, followed by treatment of the resulting aldehyde **12** with the Ohira–Bestmann reagent (**13**),[12] furnished terminal alkyne **14** in 96% yield over two steps.

The Sonogashira coupling between imidazole **14** and the known indole **15**[13] proceeded regioselectively to afford **16** in good yield (Scheme 4). After removal of the Boc group under basic conditions, a zinc-mediated partial reduction of the alkyne was performed to generate *cis*-olefin **17**. Installation of the nitrogen atom at the 3-position of the indole was carried out by treatment of **17** with sodium hydride and benzenediazonium tetrafluoroborate[14] to afford diazo coupling product **18**. Reduction of the azo group of **18** with zinc, followed by nosylation of the resultant, unstable 3-aminoindole furnished **19** in good yield. After selective deprotection of the primary hydroxy group, the crucial intramolecular Mitsunobu reaction was investigated. Gratifyingly, treatment of **20** with TMAD and nBu_3P[15] in toluene, heated to reflux, resulted in formation of the requisite ten-membered ring to give **21** in good yield without appreciable dimerization.

Having established an efficient route to **21**, we next focused on construction of the spiro β-lactam (Scheme 5). Removal of the nosyl group, followed by condensation of the resultant amine with bromoacetic acid, gave bromoacetamide **22** in excellent yield. The requisite intramolecular alkylation proceeded smoothly upon treatment of **22** with cesium carbonate in MeCN/THF (2:1) at 50°C, thus affording a spiro β-lactam as a single diastereomer. Removal of the TBS group with TBAF gave alcohol **23**.

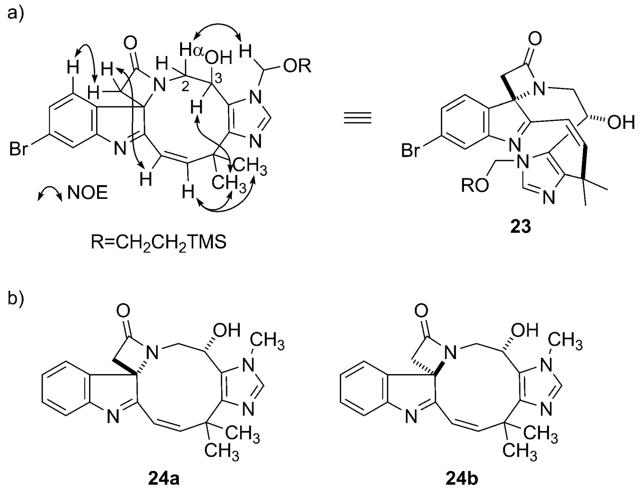


Scheme 4. a) $[Pd_2(dba)_3]\cdot CHCl_3$, Ph_3P, CuI, $nBuNH_2$, toluene, reflux, 93%; b) NaOMe, THF/MeOH (5:1), 0°C, 97%; c) Zn, conc. HCl, MeOH, reflux, 72%; d) PhN_2BF_4, NaH, THF/DMF (3:1), 0°C, 94%; e) Zn, NH_4Cl, EtOH, RT, 96%; f) *p*-NsCl, pyridine, CH_2Cl_2, 0°C, 81%; g) CSA, MeOH, 50°C, 98%; h) TMAD, nBu_3P, toluene, reflux, 75%. Boc = *tert*-butoxycarbonyl, CSA = 10-camphorsulfonic acid, dba = dibenzylideneacetone, DMF = *N*,*N'*-dimethylformamide , THF = tetrahydrofuran, TMAD = *N*,*N*,*N'*,*N'*-tetramethylazodicarboxamide.



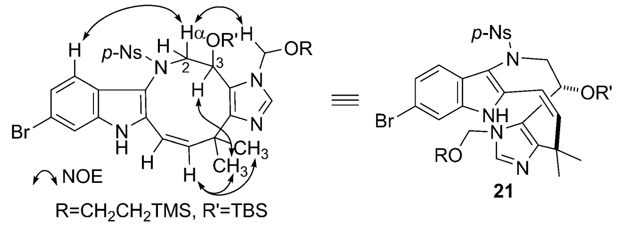
Scheme 5. a) $HSCH_2CO_2H$, DBU, MeCN, RT; b) $BrCH_2CO_2H$, EDCI·HCl, CH_2Cl_2, RT, 95% (2 steps); c) Cs_2CO_3, MeCN/THF (2:1), 50°C; d) TBAF, THF, RT, 74% (2 steps). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, TBAF = tetra-*n*-butylammonium fluoride.

The stereochemistry of **23** was determined by a combination of NMR techniques and computational chemistry.[16] The observed NOEs are shown in Scheme 6a. The coupling constant between H2α and H3 was 12.8 Hz, thus indicating that these two protons are oriented *anti* to each other. An exhaustive conformational search of **24a** and **24b** using the Conflex program generated 17 and 18 possible confomers of **24a** and **24b**, respectively (Scheme 6b). Among these conformers, only the conformers of **24a** having folded structures similar to those of natural chartellines could fully explain the observed NMR data. In addition, DFT calculations for a set of conformers of **24a** suggested that energetically favorable conformers have folded structures, which comprised > 99% of the Boltzmann distribution. Thus, we concluded that **23** has the structure shown in Scheme 6a. We also analyzed the conformation of the key intermediate **21** based on NMR data. The observed NOEs and the coupling constant between H2α and H3 (10.3 Hz) strongly suggested that **21** also has a folded



Scheme 6. Determination of the structure of **23**. a) Observed NOEs. b) Structures used for conformational analysis with the Conflex programme.

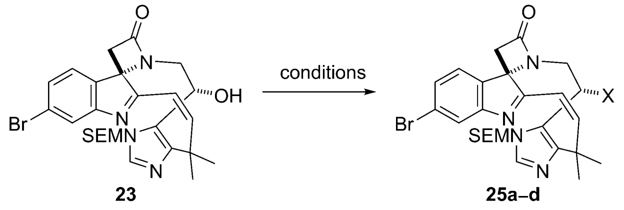
structure, as shown in Scheme 7. Taken together, these analyses imply that the intramolecular alkylation was likely to occur from the less-hindered convex side of the ten-membered ring.



Scheme 7. Selected NOEs of **21**.

Having established an efficient synthesis of the β-lactam moiety, we turned our attention to construction of the enamide moiety by elimination of the secondary hydroxy group (Scheme 8). Although treatment of **23** with either MsCl or $SOCl_2$ afforded chloride **25a**, any attempts to perform dehydrochlorination under basic conditions proved unsuccessful. Treatment of **23** with Martin sulfurane, a reagent used for dehydration either through the E1 or E2 mechanism,[17] resulted in formation of substitution product **25b**. This outcome might be attributed to the poor overlap of the orbitals of the carbocation and C–H bond, or the C–O and C–H bonds. Therefore, dehydration through a *syn* elimination was next attempted. Upon treatment with Burgess reagent, **23** only underwent a substitution reaction, instead of formation of the desired double bond. Although a 2-nitrophenylselenyl group could be introduced using the Grieco–Nishizawa protocol,[18] subsequent oxidation with H_2O_2 induced substitution with water to give **23**. This result suggested that the imidazole ring participated in generation of a carbocation upon activation of the leaving group.

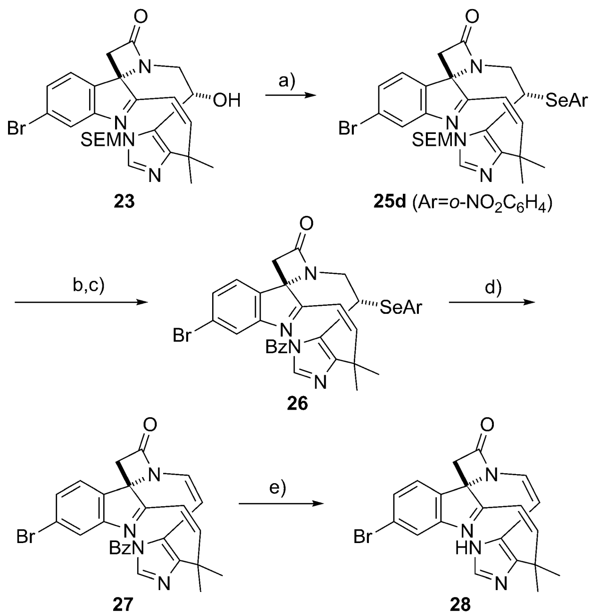
To suppress the participation of the imidazole group in the carbocation formation, an electron-withdrawing group was



conditions	product	X
MsCl, Et_3N	**25a**	Cl
$SOCl_2$	**25a**	Cl
Martin sulfurane	**25b**	$OC(CF_3)_2Ph$
Burgess reagent	**25c**	$NHCO_2Me$
o-$NO_2C_6H_4SeCN$, $n$$Bu_3P$	**25d**	$SeC_6H_4$$o$-$NO_2$

Scheme 8.

introduced to the imidazole ring (Scheme 9). After cleavage of the SEM group by treating compound **25d** with triflic acid in dichloromethane, a benzoyl group was introduced under



Scheme 9. a) o-$NO_2C_6H_4SeCN$, $n$$Bu_3P$, THF, RT, 62%; b) TfOH, CH_2Cl_2, −78 to 0°C; c) BzCl, Et_3N, DMAP, CH_2Cl_2/THF (2:1), RT, 72% (2 steps); d) *m*CPBA, CH_2Cl_2, RT, 80%; e) Na_2CO_3, THF/H_2O (2:1), RT, 63%. Bz = benzoyl, DMAP = 4-(dimethylamino)pyridine, *m*CPBA = *m*-chloroperbenzoic acid.

standard conditions to afford **26**.[19] As expected, oxidation of **26** with *m*CPBA afforded enamide **27** in good yield. Removal of the benzoyl group under basic conditions then furnished **28**.[20]

In conclusion, we have developed an efficient synthetic route to the core skeleton of chartelline C (**3**); this route features an intramolecular Mitsunobu reaction of a nosyl amide, stereoselective construction of a β-lactam, and formation of an enamide moiety by a selenoxide elimination. The stereochemistry of the alkylation for the formation of the β-lactam was effectively controlled by the secondary alcohol on the ten-membered ring. These findings suggest that preparation of the imidazole unit in an enantioselective manner would lead to an asymmetric synthesis of optically active chartelline.

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[19] While introduction of the benzoyl group was completely regioselective, the position could not be determined by observed NOE analysis.

[20] It should be noted that **28** was stable and no decomposition or hydration was observed once it was isolated and purified.

Natural Products

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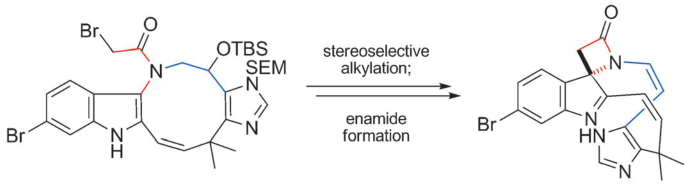
Synthetic Studies on Chartelline C: Stereoselective Construction of the Core Skeleton



What a core-ker! The title synthesis was achieved using a route featuring an intramolecular Mitsunobu reaction of a nosyl amide, stereoselective construction of the β-lactam, and formation of an enamide moiety by selenoxide elimination. The stereochemistry of the alkylation for the formation of the β-lactam was controlled by a secondary hydroxy group on the ten-membered ring. SEM = 2-(trimethylsilyl)ethoxymethyl; TBS = *tert*-butyldimethylsilyl.

