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Preliminary feasibility studies on total synthesis of the unusual marine bryozoan alkaloids chartellamide A and B

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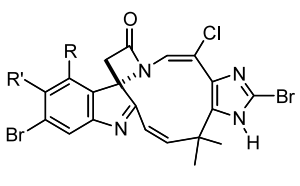
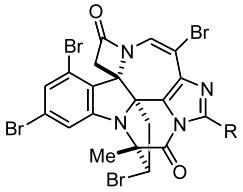
Abstract—A strategy for synthesis of the chartellamide marine alkaloids has been tested in a model, leading to the polycyclic ring system of the natural product, but which unfortunately does not provide the requisite C-9,20 relative stereochemistry.

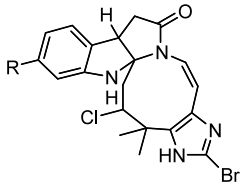
Chartellines A (**1**), B (**2**), and C (**3**) are members of a small group of about a dozen highly halogenated indole–imidazole alkaloids containing a β-lactam which are produced by the marine bryozoan *Chartella papyracea* collected in the North Sea.[1a–c] Two biogenetically-related alkaloids containing β-lactam rings are chartellamides A (**4**) and B (**5**), produced by the same organism.[1d] In addition, several congeneric alkaloids exist where the β-lactam has been rearranged to a γ-lactam, such as in securamines A (**6**), B (**7**), C (**8**), and D (**9**).[1e,f] The alkaloids in this class are all most likely derived in Nature from tryptophan, histidine, and one isoprene unit. These complex metabolites have very challenging structures from a synthetic viewpoint since they incorporate a number of unprecedented functional group arrays. We are currently attempting to develop strategies for total synthesis of both the chartellines and chartellamides and in this communication describe some of our initial feasibility studies towards the latter metabolites. To our knowledge the only previous synthetic work in this area is our report on studies leading to synthesis of the chartellines **1**–**3**.[2]



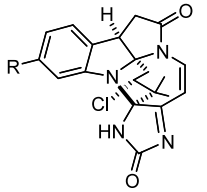
1 R, R' = Br (chartelline A)
2 R = Br, R' = H (chartelline B)
3 R, R' = H (chartelline C)



4 R = H (chartellamide A)
5 R = Br (chartellamide B)



6 R = H (securamine A)
7 R = Br (securamine B)



8 R = Br (securamine C)
9 R = H (securamine D)

Initial studies were aimed at both developing the chemistry to construct the unique ring system of the marine metabolites **4** and **5**, and to investigate important stereochemical issues related to the synthetic strategy. We have been exploring an approach to synthesis of the chartellamides outlined retrosynthetically in Scheme 1. Thus, one might simplify **4** by breaking the indicated bonds to afford a structure **10** bearing an α,β-unsaturated ester-containing sidechain at the quaternary center C-9. The C-9 allyl group in structure **11** could potentially serve as a precursor to this unsaturated ester functionality via the application of a Grubbs olefin cross metathesis with methacrylate.[3] The plan was to generate an equivalent of bis-imine **12** and to then introduce the β-lactam and allyl groups with the requisite chartellamide C-9,20 stereochemistry to produce **11**. In addition, for simplicity we have chosen at the outset to investigate a model system where the imidazole moiety of alkaloids **4** and **5** has been replaced by a benzene ring.

Thus, known isatin ketal **13**[4] was converted to the *N*-Boc derivative **14** and subsequently combined with 2-lithio styrene to afford adduct **15** in high yield

Keywords: Staudinger cycloadditions; azetidinones; imines; alkaloids; marine metabolites.

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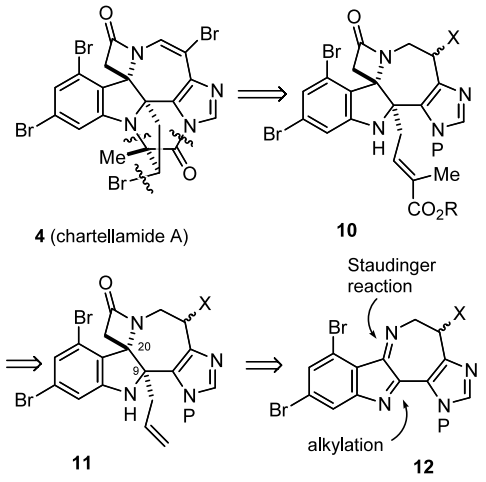
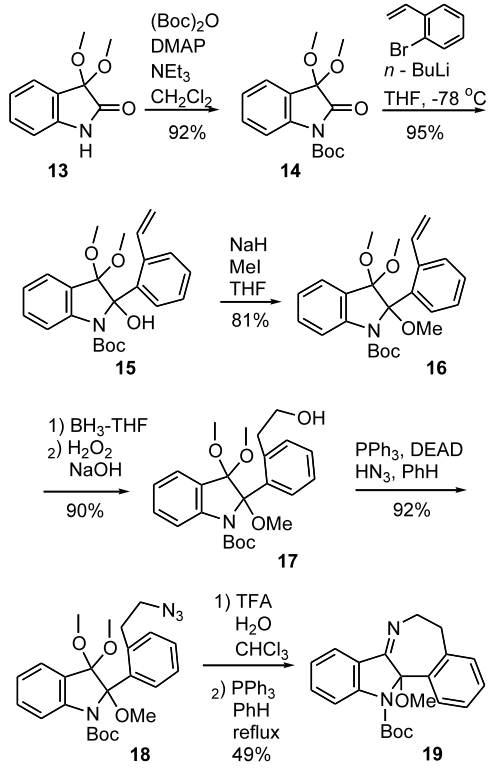
(Scheme 2). This intermediate was then *O*-methylated to form methoxy olefin **16**, which was cleanly hydroborated, producing primary alcohol **17**. A Mitsunobu reaction of alcohol **17** served to generate ketal azide **18** which could be hydrolyzed to the corresponding keto azide, and then cyclized to the desired seven-membered ring imine **19** by treatment with triphenylphosphine.[5]

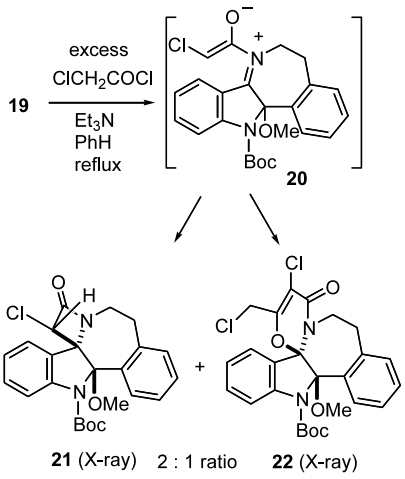
With the key imine **19** in hand, we next investigated construction of the chartellamide β-lactam system via a Staudinger reaction.[6] The cycloaddition of cyclic imine **19** with chloroketene, generated in situ from chloroacetyl chloride and triethylamine, proved to be



Scheme 1.



Scheme 2.



Scheme 3.

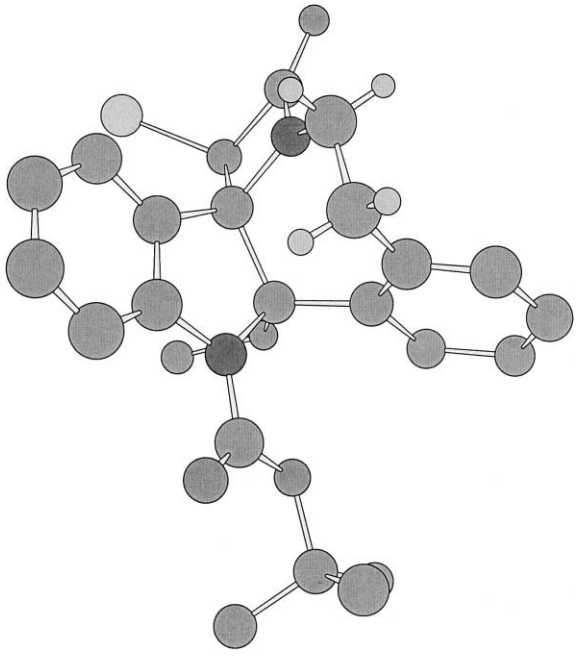


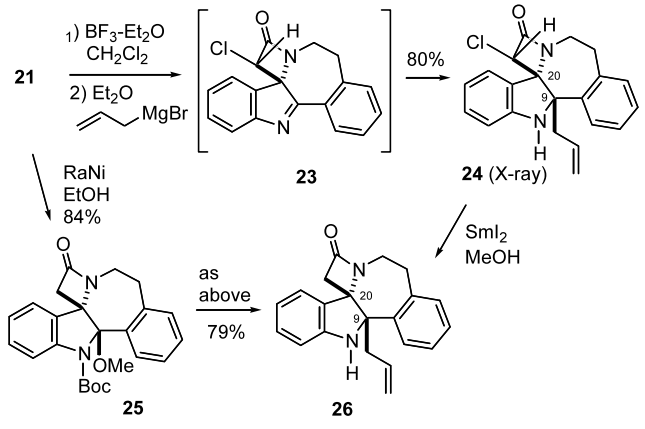
Figure 1. Chem-3D structure of α-chloro-β-lactam **21**.

quite sluggish. After some experimentation, it was found that slow addition of a large excess (10 equiv.) of chloroacetyl chloride to a solution of imine **19** in refluxing benzene containing 10 equiv. of triethylamine afforded the desired chloro β-lactam **21** along with oxazine **22**[7] in a 2:1 ratio in 85% combined yield (Scheme 3). Since this is only a model system, no serious attempt was made here to fully optimize the Staudinger cycloaddition for the β-lactam.[8] Compounds **21** and **22** were not chromatographically separable, but the β-lactam could be obtained sufficiently pure for use in the next step by fractional crystallization. Both adducts **21** and **22** were obtained as single stereoisomers whose complete stereostructures were established to be as shown by X-ray crystallography.[9,10] A Chem-3D representation of the crystal structure of **21** is depicted in Figure 1.

It seems likely that imine **19** reacts with chloroketene to initially produce a zwitterion **20**,[11] which for steric reasons probably closes slowly to β-lactam **21**. This intermediate likely has a long enough lifetime that it reacts with excess chloroketene or chloroacetyl chloride leading to oxazine **22**.[7] Interestingly, reaction of imine **19** with 10 equiv. of chloroacetyl chloride and 5 equiv. of triethylamine leads exclusively to oxazine **22**, suggesting that the condensation with zwitterion **20** involves the acid chloride rather than the ketene.

We next turned to introduction of an allyl group at C-9 of our system. It was found that treatment of compound **21** with boron trifluoride etherate leads to imine **23** (Scheme 4). This imine can be isolated if desired, but it is preferable to simply generate it in situ and add allylmagnesium bromide, leading to a single stereoisomeric alkylation product **24**. The structure of this compound was firmly secured by X-ray crystallography.[9,10] Although we were pleased that this reaction was indeed stereoselective, unfortunately the product **24** has the incorrect C-9,20 relative stereochemistry for the chartellamides. We believe imine **23** exists in a conformation where the ethylene bridge of the seven-membered ring blocks the α-face of the molecule. Such a conformation is probably similar to the one that can be seen in the X-ray structure of precursor **21** (Fig. 1). In an attempt to explore whether removal of the chlorine might possibly change the situation, α-chloro-β-lactam **21** was reduced with Raney nickel to β-lactam **25**. Allylation of this compound as was done for **21** led to a single product **26** which still has the incorrect configuration. The structure of β-lactam **26** was confirmed by interconversion with chloro β-lactam **24** by dechlorination with samarium iodide.

In conclusion, although the strategy outlined here allows for efficient construction of the polycyclic ring system of the chartellamides, it does not appear to be amenable to setting the requisite C-9,20 stereochemistry of the alkaloids. We are presently using what was learned here in devising alternative strategies to solve this stereochemical problem.



Scheme 4.

Acknowledgements

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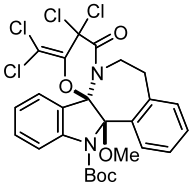
References

1. (a) Chevolot, L.; Chevolot, A.-M.; Gajhede, M.; Larsen, C.; Anthoni, U. *J. Am. Chem. Soc.* **1985**, *107*, 4542; (b) Anthoni, U.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 4709; (c) Nielsen, P. H.; Anthoni, U.; Christophersen, C. *Acta Chem. Scand.* **1988**, *B42*, 489; (d) Anthoni, U.; Bock, K.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 5638; (e) Rahbaek, L.; Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Petersen, B. O. *J. Org. Chem.* **1996**, *61*, 887; (f) Rahbaek, L.; Christophersen, C. *J. Nat. Prod.* **1997**, *60*, 175.
2. (a) Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631; (b) Lin, X. Ph.D. Thesis, The Pennsylvania State University, 2002.
3. Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
4. Wenkert, E.; Hudlicky, T. *Synth. Commun.* **1977**, *7*, 541.
5. Lambert, P. H.; Vaultier, M.; Carrie, R. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1224.
6. For reviews of the Staudinger reaction, see: Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223 and references cited therein.
7. For formation of related by-products in Staudinger reactions, see: Sohar, P.; Stajer, G.; Pelczer, I.; Szabo, A. E.; Szunyog, J.; Bernath, G. *Tetrahedron* **1985**, *41*, 1721; Afonso, A.; Rosenblum, S. B.; Puar, M. S.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 7431.
8. The reaction of imine **19** with ketene generated from acetyl chloride/NEt_3 does not produce a β-lactam. Moreover, reaction of **19** with dichloroketene from dichloroacetyl chloride gives an unstable product tentatively assigned structure **A**, but none of the desired β-lactam.



A

9. We are grateful to Dr. Hemant Yennawar for X-ray analyses.
10. X-ray data has been deposited with the Cambridge Crystallographic Data Centre (**21**: CCDC 204598; **22**: CCDC 204739; **24**: CCDC 204740).
11. See: Venturini, A.; Gonzalez, J. *J. Org. Chem.* **2002**, *67*, 9089 and references cited therein.