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Model studies on total synthesis of the chartellines, spirocyclic β-lactam alkaloids from a marine bryozoan

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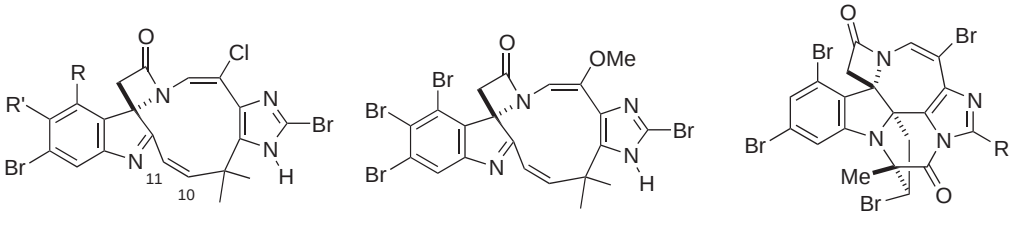
Abstract—A chartelline alkaloid model system containing a spirocyclic β-lactam moiety and α,β-unsaturated imine has been constructed from isatin using a Staudinger imine–ketene cycloaddition and an addition to an *N*-activated γ-lactam as key steps.

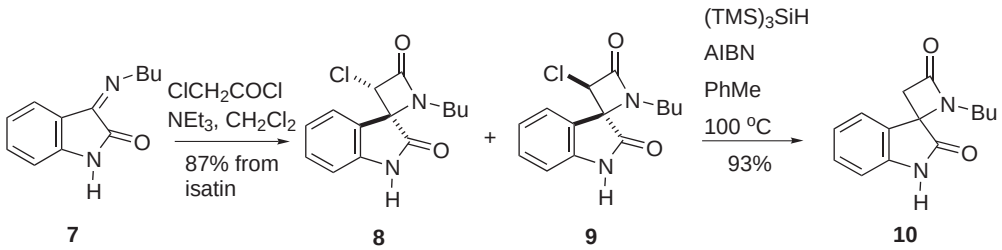
Chartellines A (**1**), B (**2**), C (**3**) and methoxydechlorochartelline A (**4**, possibly an artifact of isolation) are members of a small group of highly halogenated indole–imidazole alkaloids containing a β-lactam which are produced by the marine bryozoan *Chartella papyracea* and are collected in the North Sea.[1a,b] These unusual natural products, whose structures and absolute configuration were determined by a combination of spectral methods and X-ray crystallography, also contain a rigid ten-membered tub-shaped ring. Two biogenetically-related alkaloids containing similar spiro β-lactam rings are chartellamides A (**5**) and B (**6**), produced by the same organism.[1c,d] These complex metabolites have very challenging structures from a synthetic point of view since they incorporate a number of unique functional group arrays. To our knowledge no synthetic work has been reported in this area to date. We are currently attempting to develop a strategy for total synthesis of the chartellines and in this communication describe some of our preliminary feasibility studies.



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

4 (methoxydechlorochartelline A)

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



7 **8** **9** **10**

Scheme 1.

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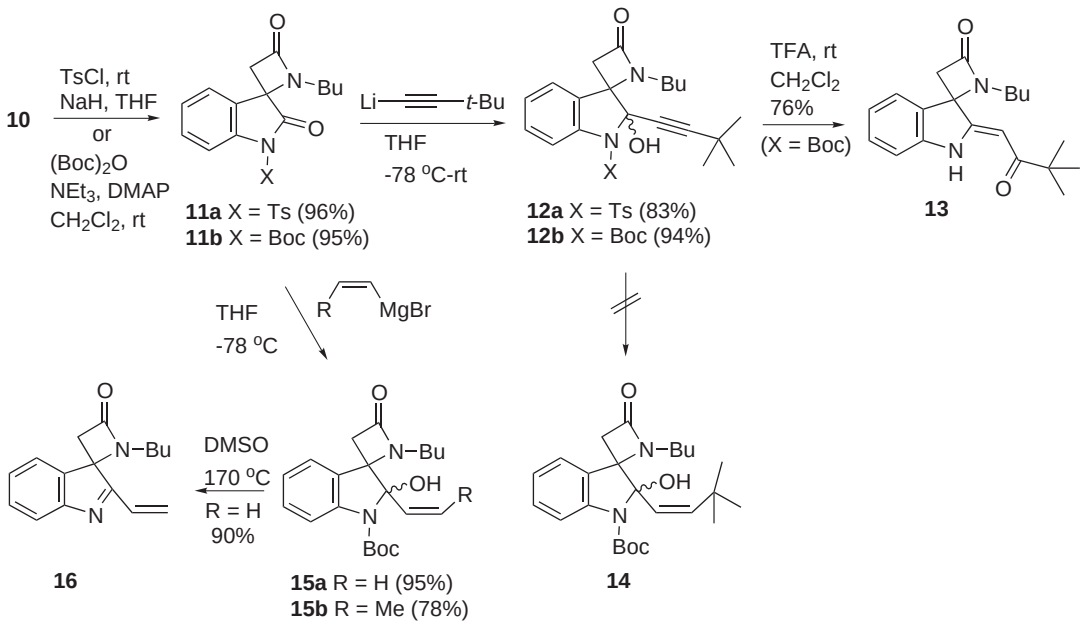
We have opted to construct the spirocyclic β-lactam ring of these alkaloids via a Staudinger ketene–imine cycloaddition.[2,3] Thus imine **7**, prepared from isatin and *n*-butylamine, was found to undergo smooth cycloaddition with chloroketene, generated in situ from chloroacetyl chloride and triethylamine,[3b] to afford a high yield of a mixture of stereoisomeric α-chloro β-lactams **8** and **9** (3:1 ratio) (Scheme 1). Attempted dechlorination of the mixture with zinc–HOAc[4] proved unsuccessful, and only the recovered starting material was obtained. Free radical reduction of the mixture of **8**/**9** with tributyltin hydride[5] did in fact lead to the desired β-lactam **10**, but it has proven more convenient and efficient to conduct the dehalogenation with tris(trimethylsilyl)silane.[6] Attempting the cycloaddition of imine **7** with the ketene itself, generated in situ from acetyl chloride[7] and gave β-lactam **10** but only in poor yield.

We next turned to introduction of a suitably functionalized carbon moiety into intermediate **10** intended to become the chartelline C-10, 11 double bond. Initially we tried to elaborate the molecule by converting the γ-lactam functionality of **10** to a reactive methyl imidate, triflate or iminyl chloride, but all of these attempts failed. On the other hand, lactam **10** could be converted in high yield to the *N*-tosyl lactam **11a** (Scheme 2). We were pleased to find that this tosylation provides sufficient carbonyl activation that addition of lithio *t*-butylacetylide to **11a** is completely chemoselective, affording the desired adduct **12a** as a 1:1 mixture of diastereoisomers. Similarly, the *N*-Boc lactam **11b**, which could be prepared from **10** in high yield, also undergoes clean and selective *t*-butylacetylide addition to provide adduct **12b** (1:1 mixture of stereoisomers).[8] Interestingly, attempted trifluoroacetic acid-promoted cleavage of the Boc group of **12b** led to the vinylogous amide **13** via a Meyer–Schuster rearrangement.[9]

A number of attempts were made to effect a Lindlar reduction of alkyne **12b** to produce *Z*-olefin **14**, but in general either starting material was recovered or the undesired totally saturated product was obtained. Hydroboration of **12b** similarly failed. Alternatively, vinylmagnesium bromide could be added to lactam **11b** to afford the requisite adduct **15a** in high yield as an inseparable 3:2 mixture of diastereomers. Similarly, *Z*-1-lithiopropene (prepared from commercially available *Z*-1-bromopropene and *t*-butyllithium) could be converted to the corresponding Grignard reagent and then added to *N*-Boc lactam **11b** to produce adduct **15b**, again as an inseparable 3:2 mixture of diastereomers. Subjection of these mixtures to TFA in an attempt to remove the Boc group and dehydrate to form the corresponding α,β-unsaturated imine led to complex mixtures of products in which the β-lactam ring was lost, presumably via rearrangement to a 5,5-ring system. However, thermolysis of Boc compound **15a** in DMSO did indeed lead to the desired unsaturated imine **16**, which proved to be very sensitive and decomposes on silica gel chromatography.[10] Unfortunately, analogous thermolysis of the propenyl *N*-Boc compound **15b** led to a complex mixture of products rather than the desired imine.

In conclusion, we have been able to successfully convert isatin into a chartelline model system **16** containing the spirocyclic β-lactam and α,β-unsaturated imine functionality, two of the unique structural features found in these natural products. It should be noted that we anticipate that the rearrangement and instability problems encountered with these simple models should not occur in the authentic chartelline system due to the constraints of the rigid ten-membered ring. We are currently investigating this chemistry in devising a strategy for total synthesis of the chartelline alkaloids.



Scheme 2.

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10. Formation of α,β-unsaturated imine **16**: A solution of Boc alkene **15a** (25 mg, 0.067 mmol) in 1 mL of deuterated DMSO was heated at 170°C for 0.5 h. The resulting solution was used directly for NMR analysis without purification of the imine. ^{1}H NMR (360 MHz, DMSO-d_6): δ 7.61 (d, $J=7.7$ Hz, 1H), 7.42–7.38 (m, 2H), 7.30–7.26 (m, 1H), 6.79 (dd, $J=18.1$, 11.5 Hz, 1H), 6.27 (d, $J=18.1$ Hz, 1H), 5.84 (d, $J=11.5$ Hz, 1H), 3.43 (d, $J=14.7$ Hz, 1H), 3.29 (d, $J=14.7$ Hz, 1H), 3.10–3.05 (m, 2H), 1.18–0.96 (m, 4H), 0.75 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.8, 165.5, 153.3, 135.5, 130.2, 128.8, 126.8, 125.0, 122.6, 121.2, 67.5, 46.6, 41.0, 29.1, 19.5, 13.2; HRMS ($C_{16}H_{18}N_2O$) calcd 255.1497 (MH^+). Found 255.1481.