Novel Synthesis of Bromoindolenine with Spiro-β-lactam in Chartelline

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Abstract: Model compounds containing an indolenine β-lactam moiety in chartelline were synthesized by nucleophilic substitution at the nitrogen atom of O-sulfonylated hydroxamic acid prepared from 2-methylindole-3-acetic acid.

Key words: chartelline, indole, β-lactam, cyclization, marine natural product

Chartelline A (**1**) and its analogs were isolated by Christophersen and co-workers from marine bryozoan *Chartella papyracea* collected in the North Sea. X-Ray and spectroscopic analyses determined them to be unprecedented unique structures comprising a highly unsaturated 10-membered ring fused with polybrominated indolenine spiro-β-lactam and bromoimidazole (Figure 1).[1] The extraordinary novel structure prompted us to initiate synthetic studies directed towards the total synthesis of chartellines.[2]

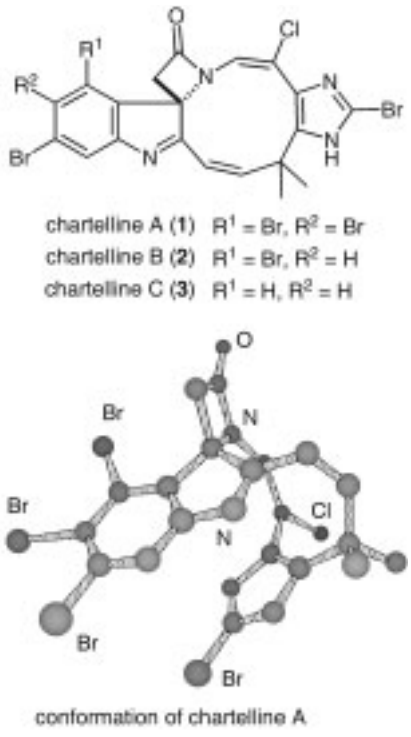

Figure 1 Structure and conformation of chartelline.

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In the course of our synthetic studies, we have reported the synthesis of a model compound **4** (R = Me) containing oxindole-β-lactam and its enamide **5** (R = Me) for chartelline (Figure 2).[3] However, further elaboration of the oxindole **4** (R = Bn or MOM)[4] to the indolenine structure with a substituent at the 2-position proved to be difficult, because of instability of the β-lactam under deprotection conditions of the Bn or MOM group.

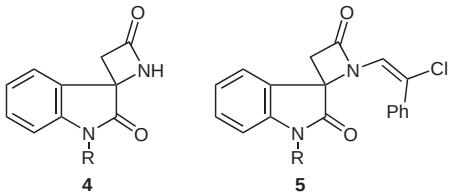
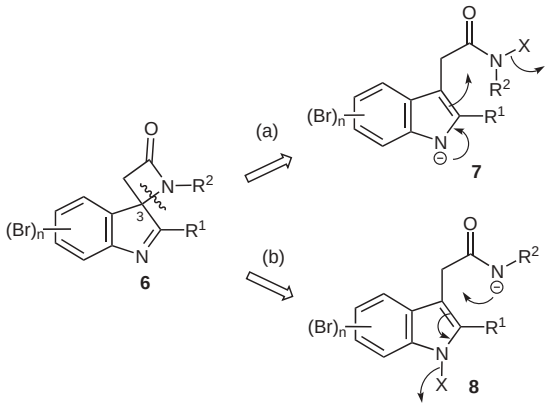


Figure 2

To overcome this problem, we considered alternative routes for the indolenine spiro-β-lactam moiety for chartelline. Retrosynthetic disconnection between C-3 and the lactam nitrogen of indolenine-β-lactam **6** led us to find two modes of cyclization as shown in Scheme 1: (a) nucleophilic substitution at the amide nitrogen with the C-3 position of indole **7**, (b) nucleophilic addition of an amide anion to the C-3 position of indole **8** bearing a leaving group at N-1 (e.g. 1-hydroxyindole derivative).[5] These routes were particularly attractive because two important functional groups such as indolenine and β-lactam would arise from the simple indole derivative at the same time. The type (b) of β-lactam formation has been employed in the synthesis of the β-lactam antibiotics such as penicillin and cephalosporin,[6] while few examples for the type (a) reaction have been reported to date. To our knowledge, only one example of the type (a) β-lactam formation was reported by Scott.[7] From these two possibilities, we now describe the successful realization of the type (a) reaction for the synthesis of indolenine spiro-β-lactam for chartellines.

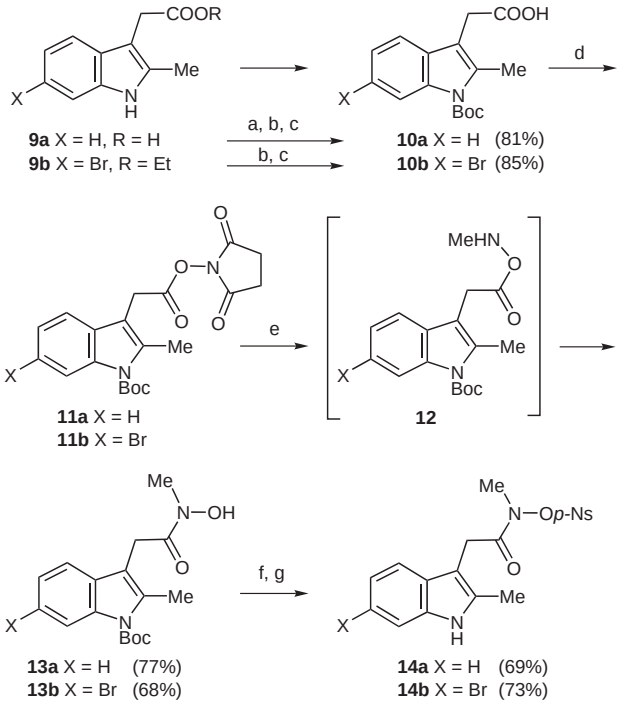
A precursor such as **7** for the type (a) β-lactam formation was synthesized from a commercially available 2-methylindole-3-acetic acid (**9a**) as shown in Scheme 2. Methylation of the carboxylic acid, protection of the indole nitrogen with a Boc group and alkaline hydrolysis of the ester[8] gave *N*-Boc-2-methylindole-3-acetic acid (**10a**) in 81% overall yield. Transformation of carboxylic acid **10a** to *N*-methylhydroxamic acid **13a** was carried out through the corresponding succinimide ester;[9] DCC



Scheme 1 Retrosynthetic analysis for indolenine β-lactam (X = leaving group).

coupling of **10a** with *N*-hydroxysuccinimide (HOSu) gave the active ester **11a**, which was subjected to reaction with MeNHOH·HCl neutralized with Et_3N. The reaction was found to proceed via an *O*-acyl compound **12** as an initial intermediate to yield *N*-acyl product **13a** in good overall yield.[10] The product **13a** was treated with *p*-nitrobenzenesulfonyl chloride (*p*-NsCl)[7] and then deprotection of the Boc group with TFA provided **14a**,[11] the precursor for β-lactam formation.

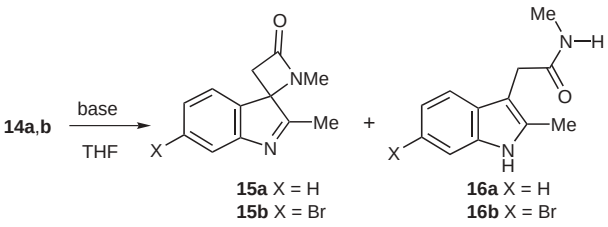
We next examined the cyclization of **14a** employing a variety of bases as shown in Table 1. When indolylmagnesium bromide prepared from **14a** and EtMgBr was refluxed in THF, an inseparable mixture of about 2:1 of



Scheme 2 *Reagents and conditions:* (a) HCl aq., MeOH, r.t.; (b) Boc_2O, DMAP, CH_2Cl_2, r.t.; (c) NaOH aq., MeOH, r.t.; (d) HOSu, DCC, Et_3N, CH_2Cl_2, 0 °C to r.t.; (e) MeNHOH·HCl, Et_3N, CH_2Cl_2, r.t.; (f) *p*-NsCl, Et_3N, CH_2Cl_2, 0 °C; (g) TFA, CH_2Cl_2, 0 °C.

the desired β-lactam **15a**[12,13] and an unexpected *N*-methylamide **16a**[14] was obtained in low yield (entry 1). The reaction with *n*-butyllithium or potassium *t*-butoxide as a base proceeded at the lower temperature, but gave a mixture of **15a** and **16a** (entries 2 and 3). We found that use of LDA improved the preferential formation of **15a** although the yield was poor (entry 4). Further screening of amide bases revealed that use of lithium hexamethyldisilazide (LiHMDS) at –78 °C was the best condition to give **15a** in moderate yield without **16a** (entry 7).

Table 1 β-Lactam Formation



Entry	**14**	Conditions		Products	
		Base	Temp	Yield (%)	Ratio (**15**:**16**)[a]
1	**14a**	EtMgBr	Reflux	31	2:1
2		*n*-BuLi	–78 °C	44	3:2
3		*t*-BuOK	0 °C	25	3:1
4		LDA	–78 °C	21	7:1
5		KHMDS	–78 °C	Complex	–
6		NaHMDS	–78 °C	19	1:0
7		LiHMDS	–78 °C	50	1:0
8	**14b**	LiHMDS	–78 °C	0	–
9		LiHMDS	–78 °C to 40 °C	26	1:0
10		LiHMDS	–78 to r.t.	62	1:0

[a] The ratios were determined by integration values of ^1H NMR spectra.

With a view to the synthesis of naturally occurring chartelline, we then examined the effect of a bromo substituent on the indole ring in the β-lactam formation. Thus, the brominated substrate **14b** was prepared from a known 6-bromo-2-methylindole-3-acetic acid ethyl ester (**9b**)[15] in an analogous manner to the synthesis of **14a** as shown in Scheme 2. In contrast to **14a**, the brominated precursor **14b** was surprisingly inert under the conditions that we had optimized; no β-lactamization was observed at –78 °C (entry 8 in Table 1), while the reaction proceeded slowly at –40 °C (entry 9). We finally found that the reaction conducted at –78 °C and then allowed to warm up to room temperature furnished 62% of β-lactam **15b** (entry 10).[16] The difference in reactivity between **14a** and **14b** might be due to the inductive effect of the bromo substituent, which decreased nucleophilicity of the anion gener-

ated from indole with the base. The structures of the indolenine-β-lactam **15a** and **15b** were confirmed by comparison of the NMR and IR spectra with those of chartelline and a model compound reported by Weinreb.[2a]

In summary, we have demonstrated a novel synthesis of indolenine spiro-β-lactam.[17] The realization of this type of β-lactam formation should open a new way to the synthesis of chartelline-type marine alkaloids. Further synthetic studies towards chartelline are currently under investigation.

Acknowledgment

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(11) Spectral Data for **14a**: Mp 144–148 °C. IR (KBr): 3367, 2914, 1773, 1715, 1534, 1349, 1193 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.29 (3 H, s, -CH_3), 3.35 (3 H, s, -N-CH_3), 3.64 (2 H, s, -CH_2-), 7.03 (1 H, br t, *J* = 7.5 Hz, indole), 7.11 (1 H, td, *J* = 7.5 Hz, indole), 7.21 (1 H, br d, *J* = 7.5 Hz, indole), 7.25 (1 H, br d, *J* = 7.5 Hz, indole), 7.84 (1 H, br s, N*H* of indole), 8.09 (2 H, br d, *J* = 9.0 Hz, phenyl), 8.21 (2 H, d, *J* = 9.0 Hz, phenyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 29.5, 39.5, 103.0, 110.4, 117.6, 119.7, 121.6, 124.1, 127.4, 128.1, 129.0, 130.7, 132.9, 135.0, 139.3, 151.2, 174.7. HRMS (FAB): *m/z* calcd for $C_{18}H_{18}N_3O_6S_1$ [M + H]: 404.0916. Found: 404.0933.

(12) Data for **15a**: IR (KBr): 3423, 2956, 1763, 1589, 1459, 1377 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (3 H, s, -CH_3), 2.57 (3 H, s, -N-CH_3), 3.26 (1 H, d, *J* = 15.0 Hz, -C$H_A$$H_B$-), 3.32 (1 H, d, *J* = 15.0 Hz, -CH$_A$$H_B$-), 7.27 (1 H, br t, *J* = 7.5 Hz, indole), 7.38 (1 H, d, *J* = 7.5 Hz, indole), 7.42 (1 H, td, *J* = 7.5 Hz, indole), 7.54 (1 H, d, *J* = 7.5 Hz, indole). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 26.7, 46.1, 69.1, 120.9, 122.2, 126.3, 130.4, 133.5, 154.2, 165.8, 180.4. HRMS (FAB): *m/z* calcd for $C_{12}H_{13}N_2O_1$ [M + H]: 201.1028. Found: 201.1000.

(13) In contrast to the report by Weinreb (2-vinyl substituent instead of 2-methyl substituent) (ref.[2a]), products **15a** and **15b** were stable enough to purify on silica gel chromatography.

(14) *N*-Methylamide **16a** was separated as its Boc derivative from the mixture of **15a** and **16a** with Boc_2O and DMAP. The structure of **16a** was determined by the following spectroscopic data. IR (KBr): 3296, 2976, 2933, 1732, 1653, 1541, 1459, 1358, 1324, 1137 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.70 (9 H, s, -Boc), 2.55 (3 H, s, -CH_3), 2.71 (3 H, d, *J* = 5.0 Hz, -NH-CH_3), 3.65 (2 H, s, -CH_2-), 5.50 (1 H, br s, -N*H*-Me), 7.22–7.32 (2 H, m, indole), 7.41 (1 H, br d, *J* = 7 Hz, indole), 8.12 (1 H, br d, *J* = 8.0 Hz, indole). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 26.4, 28.3, 32.0, 84.2, 111.6, 115.6, 117.8, 123.0, 124.1, 129.3, 135.7, 135.8, 150.5, 170.9. HRMS (FAB): *m/z* calcd for $C_{17}H_{23}N_2O_3$ [M + H]: 303.1709. Found: 303.1672.

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(16) Data for **15b**: IR (KBr): 3312, 2928, 1762, 1586, 1456, 1377 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (3 H, s, -CH_3), 2.55 (3 H, s, -N-CH_3), 3.23 (1 H, d, *J* = 15.0 Hz, -C$H_A$$H_B$-), 3.30 (1 H, d, *J* = 15.0 Hz, -CH$_A$$H_B$-), 7.24 (1 H, d, *J* = 8.0 Hz, indole), 7.41 (1 H, dd, *J* = 8.0, 1.5 Hz, indole), 7.67 (1 H, d, *J* = 1.5 Hz, indole). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 26.8, 46.1, 69.0, 123.2, 124.0, 124.4, 129.1, 132.5, 155.5, 165.3, 182.2. Anal. Calcd for $C_{12}H_{11}BrN_2O$: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.64; H, 4.05; N, 10.01.

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